The efficacy of treatment of Age-Related Macular Degeneration with antioxidant supplementation

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Age-related macular degeneration (ARMD) is the leading cause of new cases of blindness in the United States for people over the age of 65 years. In people over the age of 75 years, it is estimated that ARMD is present in 33% of this population.(1) These probably do not reflect the true percentage of patients with this disease since it has been estimated that patients lose approximately 80% of their photoreceptors before one line of Snellen acuity is lost. The disease is often classified into one of two categories. There is the non-exudative (dry-atrophic) form which occurs in approximately 90% of patients afflicted with ARMD and is considered to be the more stable form of the disease. The exudative (wet-neovascular) form occurs in the remaining 10% of patients, however, according to the Framingham Eye Study, 79% of the patients with ARMD and visual acuities of 6/60 or worse had the exudative form.(2) Because this segment of the population is steadily growing, the visual consequences to a large number of people will be enormous, representing a major public health problem. It is estimated that 7.5 million adult Americans will have vision loss secondary to ARMD by the year 2020.(3) There have been many articles and studies done to determine if supplementation with an antioxidant/vitamin/mineral therapeutic approach is beneficial in managing and/or preventing ARMD.

To understand why this supplemental approach has received so much attention, it is important to understand what is currently known about the pathogenesis of ARMD and the biochemistry involved. From a clinical standpoint, non-exudative ARMD is seen as areas of alteration in the retinal pigment epithelium (RPE) near the macular area. This can include areas of granularity, depigmentation, hyperplasia, atrophy, and drusen. In addition, the exudative form is characterized by areas of RPE detachment and choroidal neovascularization. These signs allow the clinician to recognize and diagnose ARMD, but it is also very important to understand how these signs develop over time.

Exposure to solar-ultraviolet (UVR) radiation, is believed by some to be one of the leading precursors to the development of ARMD. Short wavelength-high energy light which consists of ultraviolet and blue light is thought to be the most damaging to ocular tissues. The energy absorbed from this light can form harmful free radicals. These free radicals consist of highly reactive atoms or molecules which have one or more unpaired electrons, and will attempt to stabilize themselves by reacting with other molecules. In the process, these molecules will often become free radicals themselves, thus perpetuating a chain reaction. Although free radicals are produced by normal

biochemical processes, they are capable of damaging cellular membrane lipids, proteins, DNA and disturbing electrolyte balance.

To combat the damage done by these free radicals, the body has a number of defenses against their effects. Most prominent among these defenses are the body's antioxidants which are able to inactivate free radicals without becoming free radicals themselves. These include vitamin C, vitamin E, and beta carotene. In addition, there are a number of biological enzymes which convey antioxidant protection such as superoxide dismutase, glutathione peroxidase, and catalase.

It is known that the cornea absorbs 100% of UVC (100-290 nm) and that the crystalline lens absorbs UVB (290-320 nm). As the lens ages, absorption increases to include most UVR below 370 nm, however, there is still a significant amount of UVR absorbed by ocular tissues. At even greater risk are aphakes and pre-1984 pseudophakes who received intraocular lenses without the protection of ultraviolet coatings. Reanalysis of the Chesapeake Bay watermen studies revealed an association between increased duration of exposure to visible and blue light and more severe cases of ARMD.(4)

Because the retina contains a high concentration of

polyunsaturated lipids, is metabolically very active and is exposed to large amounts of oxygen and light, there is the potential for oxidative damage. The outer segments of the photoreceptors are susceptible to attack from free radicals because of their structure. Outer segments consist of stacks of discs rich in polyunsaturated lipids, particularly 22:6 docosahexenoic acid. Initial interaction occurs at the double bonds of the lipids themselves because these bonds serve as a supply of electrons for the free radicals. When these photoreceptor segments absorb quanta of light, they change conformation, however, excess energy is available to produce free radicals such as superoxides and lipid peroxyl radicals, which can damage the photoreceptor themselves by initiating an oxidation chain reaction of adjacent membrane lipids.(5)

In the eye, these damaged photoreceptors are phagocytized by lysosomal enzymes contained in the RPE. However, these damaged photoreceptors are not digested fully because of small differences in their structure. It is believed that the undigested remains of these photoreceptors accumulate within the RPE as lipofuscin granules which are deposited onto Bruch's membrane and are seen clinically as drusen. The presence of drusen in the retina sets the stage for the development of RPE

detachments and/or choroidal neovascularization.

Free radicals include many species derived from oxygen. These include superoxide radical, hydroperoxyl radical, hydroxyl radical, lipid peroxyl radical and singlet oxygen, which is technically not a free radical because it does not have an unpaired electron although it can cause similar damage. Instead, it contains an electron with an inverted spin on one electron. Hydrogen peroxide, which is also not a free radical, is considered to be a powerful oxidant. Superoxide radicals are capable of initiating a chain of lipid oxidation which increases lipofuscin accumulation.(4)

Vitamin C (ascorbic acid) is a water-soluble vitamin. It is believed that vitamin C is able to inactivate superoxide, hydroxyl radicals, and singlet oxygen.(5) Dietary supplementation with vitamin C will raise the levels of ascorbate in the retina and RPE, minimizing the damage caused by these free radicals.

Vitamin E (alpha-tocopherol) is a lipid soluble vitamin which can inactivate singlet oxygen, superoxide, lipid peroxyl radical, and is capable of halting free radical destruction of cell membrane lipids.(5) Deficiency of vitamin E has been shown to cause an increase in lipofuscin deposition in rats.(1)

Vitamin E levels have been shown to increase in the retina until 50 years and then decreases after 70 years, which may put the elderly at an increased risk for free radical damage.(6) In addition, vitamin E reduces blood viscosity and acts as a hypocholesterolemic agent, preventing the oxidation of LDL cholesterol.

Beta-carotene is a lipid soluble orange pigment produced by many plants and is effective in inactivating singlet oxygen and other free radicals. It is important to differentiate between vitamin A and beta-carotene. While beta-carotene is a precursor compound for the formation of vitamin A and acts as an antioxidant, vitamin itself does not possess antioxidant capability.

As previously mentioned, there are a number of biological enzymes which have antioxidant properties. Glutathione peroxidase is a selenium dependent enzyme which converts hydrogen peroxide to water and molecular oxygen. It is also able to reduce lipid peroxyl radicals to normal lipids. Reduced glutathione is also capable of inactivating reactive oxygen species. Glutathione reductase, which requires riboflavin for proper function, is the enzyme responsible for converting oxidized glutathione back to its reduced state.

A study including 916 patients was done to determine if there was a relationship between fasting plasma levels of retinol, vitamin C, vitamin E, and beta-carotene and ARMD. In addition, fundus photographs were taken of 827 of the subjects. At the conclusion of the analysis, only higher plasma levels of vitamin E conveyed a protective effect singularly. This protective effect was not seen in cases of severe ARMD (geographic atrophy/choroidal neovascularization). Although inreased levels of beta-carotene and vitamin C were suggestive of a protective effect, the results were not significant. In addition, a combination of vitamin C, vitamin E, and beta carotene was also protective. Specifically, macular degeneration occurs twice as often in patients with lower levels of vitamin E (alpha-tocopherol).(7)

Another study consisted of 127 patients with RPE abnormalities and soft drusen, 9 with geographic-atrophic ARMD, 31 with exudative ARMD, and 167 controls. It was found that when comparing the levels of serum tocopherols and carotenoids, patients with exudative ARMD did have lower levels of vitamin E. After controlling for cholesterol levels in all patients, this difference was no longer statistically significant. Likewise, with the exception of lycopene, there were not any differences

between serum levels of individual carotenoids in patients with ARMD and in controls. However, subjects with lower levels of lycopene were twice as likely to have ARMD.(8)

One study was conducted to determine if there was any correlation between levels of serum carotenoids (lutein, zeaxanthin, beta-carotene, cryptoxanthin, and lycopene), vitamin C, vitamin E, selenium and incidence of exudative ARMD. There were a total of 421 patients with exudative ARMD amd 615 controls. It was found that subjects in the medium and highest percentile groups in terms of carotenoid blood levels had reduced risk of ARMD compared to patients in the lowest percentile group. Although no protective benefits were found for selenium or vitamins A or E, researchers did find that persons with higher levels of an antioxidant index combining all four micronutrients had a reduced risk of neovascular macular degeneration.(2)

It has been shown that low levels of both glutathione peroxidase and glutathione reductase are associated with an increased risk of ARMD. Thirty-six subjects, consisting of 18 patients with ARMD and 18 controls had blood drawn to determine if levels of these enzymes were linked with ARMD. Blood levels of glutathione reductase were lower in patients with ARMD and further analysis of the data revealed that low levels of

glutathione peroxidase were linked with an increased risk of ARMD. There were no differences found between controls and patients with ARMD for blood levels of superoxide dismutase.(9)

Superoxide dismutase (SOD) and catalase are both enzymes which require zinc and copper to function properly. Zinc is the second most abundant trace mineral in the body, but it has the highest concentration in the eyes. Superoxide dismutase, found in photoreceptor outer segments, converts superoxide radicals to hydrogen peroxide and oxygen. Catalase converts hydrogen peroxide to water and molecular oxygen. It is also believed that catalase is involved in phagocytosis of the outer segments of photoreceptors. Catalase levels are lower in aged RPE cells and eyes with drusen. Because of their antioxidant capabilities and reliance on the metallic trace elements copper and zinc, these enzymes have been the subject of much interest.

In one of the earliest studies done on this subject, Newsome, et. al. investigated the effects of oral zinc administration on the visual acuity outcome of 151 patients with drusen and/or ARMD. Length of follow-up for patients varied from 12 to 24 months. After this time, it was found that patients treated with 100 mg zinc sulfate b.i.d had significantly less loss of visual acuity than controls receiving placebo

supplementation. Although some zinc-treated eyes suffered loss of 20 or more letters, the risk was 2.5 times greater in the placebo treated group. A comparison of fundus photographs taken at baseline and at final visit also showed that more eyes remained stable or showed less accumulation of visible drusen in the group treated with zinc supplements.(10)

In a study of 16 subjects with ARMD, researchers found that there were elevated levels of serum zinc and copper in patients with ARMD compared to 16 healthy controls. These results are inconsistent with the hypothesis that zinc deficiency may be related to the pathogenesis of ARMD. However, sample size was small, and as with all studies in which analysis of serum levels are done, it is important to remember that serum levels do not necessarily reflect actual cellular concentrations and/or indicate what effects are related to exposure time to elevated or deficient levels.(11)

As a result of these investigations, some have advocated that patients with ARMD and/or patients at risk for developing ARMD should be placed on over-the-counter (OTC) nutritional supplements. To assess whether these OTC supplements are capable of raising blood levels of certain antioxidant nutrients, namely zinc and beta carotene, Kaminski et. al. conducted a diet survey

followed by supplementation with one and then another OTC formulation. The two products compared were Ocuvite (manufactured by Lederle), and ICAPS-Plus (manufactured by La Haye Laboratories). Subjects of good general health and 55 years of age or over were required to maintain a logbook of food intake prior to the beginning of the study. Following analysis to determine the average daily intake of certain antioxidant nutrients, it was found that approximately 75% of patients were deficient in zinc and selenium and 54% were deficient in vitamin E. Patients were randomly assigned with a two week supply of one of the two tablets followed by a two week washout period. After the washout period, patients were given the other tablet to be taken for the same two week period. Both supplements were found to raise blood serum levels of zinc similarly, however, only ICAPS-Plus was found to raise beta carotene serum levels significantly. This latter finding may be attributable to the fact that ICAPS-Plus contains a higher amount of beta-carotene.(12)

Another study conducted at eight Department of Veterans Affairs Medical Centers was designed to assess whether supplementation with a broad spectrum antioxidant capsule was effective in stabilizing or improving visual performance in

patients afflicted with non-exudative ARMD. Thirty-two patients with dry ARMD were assigned to group one (placebo) and 39 dry ARMD patients were in group two (supplementation with Ocuguard). A third group of 13 age and sex matched individuals free of dry ARMD signs was selected to serve as a control group. Ocuguard (manufactured by Twin Lab, Inc.) contains 14 components including vitamins C and E, beta-carotene, bioflavonoids, riboflavin, zinc, selenium and acetyl cysteine (a precursor of glutathione). A variety of ophthalmic tests and dietary assessments were performed at 6, 12, and 18 months.(6) Distance LogMAR acuity in group 1 patients declined approximately one line Snellen acuity, while group two patients showed stabilization of distance LogMAR acuity. In addition, near M print acuity showed the same trend, with group one patients showing a decrease in near M print acuity and group 2 patients showing stabilization. Contrast sensitivity testing revealed stabilization of group 2 eyes at the end of the 18 month period, while group 1 patients experienced a decrease in contrast sensitivity. The results of this study are clearly suggestive of a protective effect of antioxidant supplementation.(13)

In the clinical setting, it is important to identify those patients who are at risk for the development of age-related

macular degeneration. Data collected from the first National Health and Nutrition Examination Survey (NHANES-1) was analyzed to determine which factors were associated with ARMD. There were a total of 3,082 persons over the age of 45 years examined, of which 178 were diagnosed as having ARMD. Risk factors for ARMD from this data include age, hypertension (elevated systolic pressure), cerebrovascular disease, ametropia-hyperopia, and reduced consumption of foods rich in vitamin A. The analysis also revealed a slight increase (not statistically significant) in males and blacks, which is confusing in that there is a common belief that ARMD is more common in females and rare in blacks.(14) Other risk factors believed to be related to ARMD include positive family history, weakness of hand grip, light-colored irides and light-colored hair, smoking, and increased exposure to solar radiation.(15)

As previously mentioned, age-related macular degeneration represents a major public health problem which will affect a large segment of the elderly population. At this point in time, there have been no definitive studies done to determine how this disease process can be prevented. Laser photocoagulation of choroidal neovascularization is a treatment option in cases of exudative ARMD and has been shown to preserve vision in patients

with this entity, however, the vast majority (90%) of ARMD patients are of the non-exudative variety. There are several new developments which will hopefully give clinicians new management/ treatment options for these patients.

There is considerable evidence in the literature to support the association between ultraviolet exposure and the development of ARMD. Therefore, regardless of age, all patients should definitely be informed of the benefits of ultraviolet protection. People are living longer these days and are thus susceptible to an increased duration of UVR exposure over their lifetime. In addition, the damaging of the ozone layer will result in even greater levels of UVR exposure in the future. This management option would reduce the damage resulting from free radical action at the earliest levels. UVR lenses also protect the patient from other disease entities believed to have an association with the cumulative effects of ultraviolet exposure, such as pterygia and cataracts.

The free radical theory of damage to human tissue has been the subject of much research and interest. The body's defense against these harmful free radicals consists of the antioxidants, including vitamins C and E, beta-carotene, and the metalloenzymes glutathione peroxidase, superoxide dismutase, and catalase, which

require the trace minerals zinc, copper, selenium, and manganese. The research reviewed in this paper appear to support the proposed theory that ARMD may have a nutritional component in its development. Although some results have been inconsistent, various papers have revealed a protective effect for elevated levels of carotenoids, vitamin E, glutathione reductase, and glutathione peroxidase.

The two double blind, placebo-controlled studies offer the most compelling evidence that nutrition likely does have an impact on ARMD. Patients receiving placebos were 2.5 times more likely to suffer vision loss than patients given zinc supplementation. The study done at the VA medical centers revealed that subjects given Ocuguard broad spectrum antioxidant supplementation showed stabilization in distance and near visual acuity and stabilized contrast sensitivity testing compared to subjects receiving placebos. Hopefully, additional larger scale studies can be done of this nature to gain a better understanding of the role which nutrition may play in the pathogenesis of ARMD.

Supplementation with zinc offers a greater clinical dillema to practitioners because it interferes with copper intake in the gastrointestinal tract. Excessive zinc causes an increase in intestinal metallothionein which binds tightly to copper,

preventing its absorption. Because copper is necessary for the production of erythrocytes, deficiency can result in copper anemia, characterized by pallor, retarded growth, edema, and anorexia. Thus, any person receiving zinc supplementation should also receive copper supplementation. Zinc can also cause gastrointestinal problems such as nausea, vomiting, and abdominal pain.(4) A dietary deficiency of zinc can lead to iron anemea, short stature and hepatosplenomegaly.(16)

Because nutrition may be linked to ARMD, appropriate dietary recommendations should be made to all patients. Patients should be instructed to eat a diet with emphasis placed on complex carbohydrates, fruits, and vegetables. Several of these studies revealed that subjects had levels lower than recommended for one or more of these antioxidants. Adjustment of diet would be expected to increase these levels. One exception would be vitamin E, which can not be obtained from normal dietary intake. Green leafy vegetables are of particular importance because they contain vitamins, minerals, carotenoids, and glutathione.

It is estimated that 33% of Americans are already taking multivitamin supplements.(17) A 1990 article states that the sale of vitamin and mineral supplements exceeds $2 billion dollars annually and is expected to increase by 15% per year for

the next decade.(18) The main concerns with antioxidant supplementation are possible toxic effects. Vitamins A and D, if taken excessively, can result in toxic effects. Zinc supplementation may result in copper anemia and gastointestinal problems. Vitamin C in high doses can also cause gastrointestinal upset and kidney stones. However, vitamins E and riboflavin are associated with very low levels of toxicity and beta-carotene, selenium, and manganese have no known toxic effects. Beta-carotene does not cause the toxic effects of vitamin A because it is slowly converted to vitamin A. Although critics are quick to look at the possible toxic effects of these supplements, all of the OTC antioxidant supplements contain quantities well below levels necessary to produce toxic effects when taken as directed.(5) However, it is important to verify what other supplements that the patient may be taking to avoid any additve effects with other medications. Because the potential visual outcome for ARMD patients can be severe, broad spectrum antioxidant supplementation is a management option which must be strongly considered, particularly in the presence of one or more of the risk factors previously mentioned. For patients with multiple risk factors and/or physical signs of ARMD, the potential benefits for their long term vision is worth the small

risk associated with supplementation. Another duty of the clinician would be to inform patients that there is no absolute proof that supplementation will be beneficial in the treatment of ARMD. It would be preferable to have indisputable evidence displaying the benefits of antioxidant supplementation, however this evidence is not available and it may be many years before it is. In the meantime, there is a large segment of the population at considerable risk for the development of ARMD with subsequent visual loss. Although the risk of toxicity is present, it is a small risk compared to the potential preservation of vision.

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