Supplementation in Age-Related Macular Degeneration

A Double-Sided Approach

Laura Solt

Micronutrient Metabolism
School of Health and Rehabilitation Science
University of Pittsburgh
2/27/2009

Introduction

Age-related Macular Degeneration

AMD is a growing problem in the aging population. It causes central vision loss by damaging the macula, located in the center of the retina. Two forms of AMD exist; wet AMD and dry AMD. Wet, advanced AMD, is caused by blood leakage from vessels under the macula causing a disruption in the macula's position (1). Wet AMD occurs quickly without pain. Dry AMD can occur in three stages and involves the buildup of drusen, which are yellow deposits under the retina (1). Early AMD has small drusen found in the retina and no noticeable change in eyesight (1). Intermediate AMD involves slightly larger drusen and a small spot of blurred central vision (1). Advanced AMD has drusen along with the destruction of light-sensitive cells in the retina leading to a greater blurred spot in central vision (1). AMD is most commonly found as the dry form but the wet form causes most of the vision loss problems. Researchers currently have been performing trials with different vitamin and mineral supplementations to see if they assist in the delay of onset or progression of AMD. The vitamins and minerals researched are vitamin C, vitamin E, β-carotene, zinc, and the antioxidants lutein and zeaxanthin. Some articles state that it is beneficial to take these supplements while other articles claim they do not prevent or delay the onset of AMD. The following paper takes a look at both sides of this argument.

Methodology

A literature search was performed using the electronic database PubMed. Initially, 12,307 articles were found using the keyword phrase *age-related macular degeneration*. To limit the large number of articles, another search was performed using the phrase *age-related macular degeneration* in conjunction with *vitamins and minerals*. This search resulted in 48 articles. After briefly scanning some of the abstracts, 10 articles were identified as potential articles to be used in this paper and were set aside. Before continuing, the search was narrowed down by applying the following limits: published in the last five years, a link to the free full text, and written in English. From this three more articles were set aside for potential use in this paper. With a total of 13 articles set aside, the author read through each abstract for their relevance to the subject and three articles were identified. Later on, the same search was performed again by changing the limits to: randomized controlled trial, case study, clinical trial, and journal article. After reading through the abstracts, this search produced one additional article. The reference list of this fourth article was reviewed to locate a final article. In total, five articles were found that pertained to the research topic and they are discussed in this paper.

Results

Supplements Involved

Vitamin C, also known as ascorbic acid, is an antioxidant only found in exogenous sources. In the human body, ascorbic acid is oxidized to its more absorbable form, dehydroascorbate. As an antioxidant, vitamin C functions as a reducing agent by donating

electrons to free radicals and various transition metals (Copper and Iron). Free radicals are molecules that lack an electron in their outer shell causing them to damage other cells within the body. By keeping the transition metals in their reduced state they are able to assist in multiple reactions including the synthesis of collagen, carnitine, tyrosine, and neurotransmitters (2, pg.314). Clearly, vitamin C performs many beneficial functions in the body. The recommended intake by the RDA is 90mg for adult men and 75mg for adult women. There is an increased intake for women who are pregnant and lactating as well as an additional 35mg for smokers (2, pg. 319-20).

Zinc is found throughout the body and functions in many different ways. It assists enzymes in their reactions, as well as providing structural integrity for proteins. Some enzymes are entirely dependent on zinc. A few of these zinc-dependent enzymes are carbonic anhydrase, alkaline phosphatase, alcohol dehydrogenase (seen in the reaction of retinol to retinal which is important for eyesight), superoxide dismutase (an antioxidant for the removal of O_2^- a free radical), as well as many others. Zinc has a high concentration in the retina due to its cofactor use in superoxide dismutase and catalase reactions (3). Zinc is also needed for cellular replication and growth, immunity, stabilizing cell structure, binding proteins to DNA, and preventing apoptosis (2, 493-495). Zinc has an RDA of 11mg for adult men and 8mg for adult women with an increased need of 11-12mg for pregnancy and lactation (2, pg. 496).

Carotenoids are derived from plants and some are precursors to vitamin A. Lutein and zeaxanthin, both carotenoids that act as antioxidants, are found within the retina and lens of the eye. They both are responsible for helping the body rid itself of free radicals, by reducing

oxidation activity, and protecting against high-energy blue light (2, 4). A precursor to vitamin A is β-carotene functions as an antioxidant by reducing oxidative activity in lipid plasma membranes and LDLs (2, pg. 386-387). However, too much beta carotene can be harmful and can also effect the plasma concentrations of vitamin E. A recommended intake of carotenoids does not exist. However, 3.6μg of β-carotene is equal to 1 IU of vitamin A (2, pg. 388).

Some research involving age-related macular degeneration (AMD) has shown that patients benefit from the intake of Vitamin C, Vitamin E, β-carotene, Lutein, and Zinc. Other studies have claimed that these vitamins, minerals, and antioxidants have no effect or benefit related to AMD. The following articles represent studies that have found no significant evidence supporting the intake of supplements to prevent AMD.

Research Evidencing No Support for Taking Supplements

In the first article, zinc is looked at in two prospective studies, one with 51,529 men ages 40-75 and the other with 121,700 women ages 30-55 (3). The study analysis narrowed down the number of subjects by including only those who were older than 50, had no signs of AMD or cancer, completed a food-frequency questionnaire (FFQ) within a year, and had taken multivitamins or zinc supplements (3). These qualifications limited the population analysis to 51,809 women and 31,530 men (3). This number was further decreased by only including those who had been diagnosed by an ophthalmologist with AMD that caused visual loss equal to or greater than 20/30 in one or both eyes (3). In the end, the study consisted of 230 women and 154 men (384 total AMD cases) who were then separated into groups according to frequency of zinc intake (3). Many lifestyle factors were taken into consideration including high blood

cholesterol, BMI, high blood pressure, age, and amount of smoking (3). Over a 10 year period, 195 subjects had the early form of AMD and 189 subjects had the late form (3). The early form is classified as one who has drusen, a yellowing of the retina, and changes in the pigment epithelial in the retina (3). The late AMD is classified as geographic break down, pigment epithelial detachment, and scaring (3). Those who smoked less had a higher intake of zinc, lutein, and zeaxanthin (3). After comparing the data of those who consumed more zinc to those who consumed less, results showed no correlation between zinc consumption and AMD. One table shows that when the median intake of zinc for women was 8.5mg/d there were 47 cases of AMD and as it reached the highest intake of zinc at 25.5mg/d there were 44 cases (3). For men, when the median intake was at its lowest of 9.9mg/d, there were a total of 27 cases of AMD. With the highest intake level of 40.1mg/d of zinc, there were 36 cases of AMD (3). (Table 1 below)

	Quintile of zinc intake						
	1	2	3	4	5	*p* trend[b]	*p* heterogeneity[c]
Total zinc							
Women							
Median intake, mg/d	8.5	10.2	11.6	13.5	25.5		
Number of cases (n)	47	44	57	38	44		
Age-adjusted RR (95% CI)	1.00	0.99 (0.65–1.49)	1.34 (0.91–1.97)	0.87 (0.57–1.34)	0.93 (0.62–1.40)	0.45	
Multivariate[d] RR (95% CI)	1.00	1.08 (0.72–1.64)	1.52 (1.03–2.26)	1.01 (0.65–1.57)	1.05 (0.69–1.59)	0.70	
Men							
Median intake, mg/d	9.9	11.9	13.6	16.4	40.1		
Number of cases	27	26	33	32	36		
Age-adjusted RR (95% CI)	1.00	1.10 (0.64–1.90)	1.41 (0.84–2.37)	1.37 (0.82–2.29)	1.27 (0.77–2.09)	0.66	
Multivariate[e] RR (95% CI)	1.00	1.06 (0.62–1.83)	1.37 (0.82–2.30)	1.28 (0.76–2.16)	1.28 (0.77–2.12)	0.53	
Pooled Multivariate RR (95% CI)							
Baseline (n = 384)	1.00	1.08 (0.77–1.50)	1.46 (1.07–2.00)	1.11 (0.80–1.56)	1.13 (0.82–1.57)	0.74	0.51
Most recent intake (n = 384)	1.00	1.08 (0.78–1.50)	1.35 (0.98–1.86)	1.17 (0.77–1.78)	1.13 (0.82–1.56)	0.94	0.40
Average intake (n = 384)	1.00	0.90 (0.65–1.25)	1.10 (0.81–1.50)	0.98 (0.50–1.93)	1.06 (0.78–1.44)	0.67	0.85
With eye exam (n = 376)	1.00	1.05 (0.75–1.46)	1.44 (1.05–1.97)	1.08 (0.77–1.52)	1.10 (0.79–1.52)	0.92	0.67
Without CVD[f] (n = 326)	1.00	1.18 (0.82–1.70)	1.62 (1.14–2.29)	1.26 (0.87–1.83)	1.24 (0.86–1.77)	0.62	0.56
Zinc from food							

Table 1. Relative risk of age-related macular degeneration across quintiles of energy-adjusted zinc intake (3)

Participants in a randomized, double-blinded, placebo-controlled trial of zinc sulfate at 100mg twice a day for two years showed a decrease in the amount of vision loss compared to the placebo group (3). However, in a second trial including the same dose, duration and design, no difference was seen in the amount of vision loss (3). Since these studies show varying results, an increased consumption of zinc at this level has no proven effect on the prevention or delay of AMD (3). To prove any evidence of the association between zinc and AMD the article explains that more research is needed including a longer time period to observe participants and a larger sample of individuals who use higher doses of zinc supplements (3).

Lutein and zeaxanthin, both carotenoids that act as antioxidants, are found within the retina and lens of the eye. They both are responsible for helping the body rid itself of free radicals and protecting against high-energy blue light (4). In this randomized control trial 6mg/day of lutein combined with retinol equivalent, vitamin C, vitamin E, zinc, and copper was given to an experimental group while a placebo was given to the control group (4). An assortment of vitamins and minerals were given because many work together within the body and together may have a greater effect on AMD (4). The participants selected for the study included those who have vision loss, have only ocular pathology in one eye if so only being ARM (early form of AMD), no subjects with AMD, no type I or II diabetes, and no anti platelet or anti coagulant medication allowed (4). The experiment went on for nine month with a baseline test followed by any changes noted (4). A total of 30 participants were divided into the two groups, one with the placebo and the other with lutein and multivitamins (4). The genders of the

participants were relatively even and the age fell between 55-82 years old (4). Between the two groups there showed no major differences in gender, baseline results, age, amount of smoking, nutritional supplementation, and visual function (4). Food diaries and food-frequency questionnaires were taken in the beginning and at the end to observe any changes in the diet during the nine months (4). The dietary results showed a significant increase of about 2.30mg/day of zinc within the experimental group, but no changes with the other vitamins and minerals (4). According to the results no major difference appeared in the development of ARM between the experimental group and the control group (4). Whereas, a different study found that by increasing the amount of vitamin C, vitamin E, β-carotene, and zinc there appeared to be a slight delay in the advance of AMD (4). It appears that the results of this experiment were not in agreement with others due to the lower amount of lutein (6mg.day) given per dose (4). More research has been occurring on the effects of lutein supplementation in AMD. A different trial illustrated that an amount of 10 or 20mg per day over a time period of 4 months showed an increased response of macular pigment optical density which is a measure of the levels of lutein in the retina (4). Some studies say an increase in lutein levels within the retina leads to a decrease in the risk of AMD (4). Overall, this random controlled trial showed no correlation between lutein and supplements with AMD (4).

Similar results occurred in a randomized, double-blind, placebo-controlled trial on the effects of β-carotene on healthy males ranging in age from 40 to 84 begun in 1982 (5). The trial took place over 12 years and involved 22,071 individuals. The main reason for the trial was to analyze β-carotene's effect on cancer and cardiovascular disease (5). Researchers then used

information collected from this trial to look at the early form of AMD, age-related maculopathy (ARM). Beta-carotene was given to the experimental group every other day in a dosage of 50mg and a placebo was given to the control group (5). In addition to β-carotene, the experimental group received a low dose of aspirin to determine if it would reduce myocardial infarction (5). After six years, aspirin proved to be statistically significant causing termination of dosage (5). All subjects participating were questioned about smoking history, alcohol intake, multivitamin intake, cholesterol, physical activity, and history of diabetes mellitus (5). Including these initial assessments, participants filled out a questionnaire every year based on their consistency with supplementation and any pertinent health condition (5). A follow-up questionnaire revealed 78% of the β-carotene group was still taking the pills at the end of the 12 years (5). A small percent of the placebo group was taking their own supplements of beta carotene and vitamin A (5). Accuracy of following the regimen of pill intake was assessed by unannounced visits to take blood plasma β-carotene levels of participants in certain areas (5). With reassurance that subjects were consistently taking their pills, the article goes on to talk about the results and further requirements. Halfway through the 12 years participants were asked whether they had been diagnosed with macular degeneration and if so what date they found out and the severity of their visual acuity (5). Researchers further questioned participants about the signs of ARM including "drusen, retinal pigment epithelium [RPE] hypo/hyperpigmentation, geographic atrophy, RPE detachment, subretinal neovascular membrane, or disciform scar (5)" along with when visual acuity became 20/30 [4]. A total of 21,142 participants were included in this study where about half took β-carotene and half took the placebo (5). Individuals from each group were compared based on four different age

groups created to keep all variables similar (5). Other factors contributed to further dividing the groups based hypertension, use of alcohol, whether they smoke, cholesterol, supplementation of multivitamins, and a few others (5). Researchers classified the ARM in three ways: visually-significant ARM (which was the primary endpoint), ARM with or without vision loss, and advanced ARM (these were considered secondary endpoints) (5). The primary endpoint was based on a diagnosis of vision loss of 20/30 or worse (5). There were 549 cases of ARM identified and of these 332 had visually-significant ARM, the primary endpoint (5). Of these 332 cases, 162 were from the β-carotene group and 170 were from the placebo group (5). Of those with advanced ARM (129 cases) 63 were from the β-carotene group and 66 were from the placebo group (5). In looking at the total cases of ARM (549) regardless of severity or vision loss, 275 were the β-carotene group and 274 were the placebo group (5). Due to the similarity in number of each case outcome and the lack of a significant p-value no correlation could be linked between supplementation of β-carotene and decreased risk of ARM.

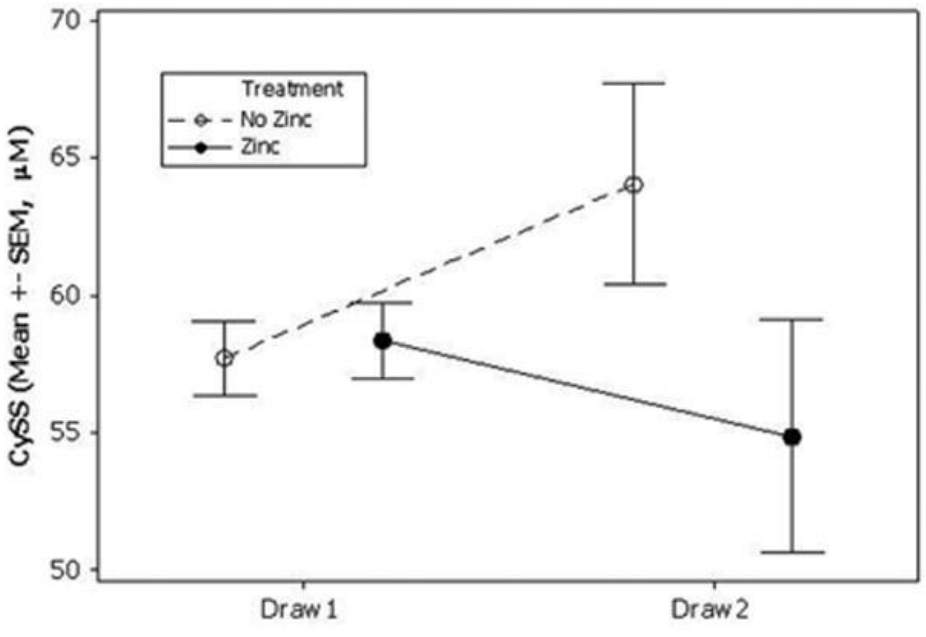
Research Supporting Supplements

The following study looks at a prospective, double-blind, 6-month trial with a group of 37 subjects receiving a supplement pill containing Taurine, Omega-3 Fatty Acids, Zinc, Antioxidant, and Lutein (TOZAL) (6). The TOZAL group data was compared to a placebo group of participants who were receiving a supplement containing 440mg vitamin C, 200 IU vitamin E, 40mg zinc, and 3,000 IU beta-carotene (6). The TOZAL group was required to come in for five visits to confirm their eligibility for the experiment, take a baseline test for their beta-carotene visual acuity (BCVA), contrast sensitivity, and to evaluate and retest at the end of the trial

period (6). Qualifications consisted of many things including but not limited to; age range of 50-90, no other nutritional supplementation allowed, and one eye with dry AMD at a certain size (6). The supplement was taken in two capsules three times a day in accommodation with meals (6). All participants had to complete a visual function questionnaire along with a daily log of the consistency of intake of the supplement pills. At the end of the trial the TOZAL group's baseline of visual acuity was compared to a follow-up test and determined to be statistically significant by a two-sided alpha of 0.05. (6). Over the six months the BCVA of the TOZAL group appeared to improve compared to the placebo group which exhibited BCVA loss (6). A total of 76.7% of the TOZAL supplement group improved or maintained visual acuity while 23.3% did not experience improvements but worsened (6). Results showed no significant change in other tests performed consisting of contrast sensitivity, visual function questionnaire, and retinal photographs (6). Occurrence of these outcomes may be due to the length of the experiment, implying that a trial of longer duration may be needed to prove greater effects of nutrient supplementation. In conclusion, the experimental group receiving the TOZAL nutritional supplements showed an increase in visual acuity compared to the placebo group (6).

The final article was about the benefits of zinc supplementation in AMD. It was a random clinical trial on levels of plasma thiol and disulfide redox status. Oxidative stress is a potential factor in the development of AMD; this research looked at the effect of antioxidants in reducing the levels of glutathione (GSH), oxidized glutathione (GSSH), cysteine (Cys), and cystine (CySS) (7). Subjects were selected from the Age-Related Eye Disease Study (AREDS) and assigned to four experimental groups; antioxidants, zinc, antioxidants plus zinc, and placebo (7).

Antioxidant doses consisted of 500mg vitamin C, 400IU vitamin E, and 15mg β-carotene. Zinc doses contained 80mg zinc oxide and 2mg cupric oxide (7). Subjects were randomly assigned a group and were within the age range of 55-80 years with AMD (7). To assess the groups they were paired together according to zinc supplementation; zinc versus no zinc (7). Zinc alone, and antioxidants plus zinc were together, and antioxidants and placebo were together. Both groups had blood drawn twice, once at the 20 month point and the second at the 80 month point (7). The first blood draw showed no significant difference in plasma concentrations (GSH/GSSG or Cys/CySS redox status) between both groups (7). The second blood draw also showed no differences in the plasma concentrations of the redox status, however, lower levels of plasma CySS concentrations with zinc versus no zinc were noted ($p = 0.01$) (7). (Figure 1 below)



(7)

A decrease in plasma GSH concentration was statistically significant ($p = 0.05$) in zinc supplementation compared to the group without zinc (7). Zinc plays an important role in this conversion because it is thought to activate an antioxidant response element (ARE) which acts on a cystine/glutamate exchanger, where cystine (CySS) is absorbed and glutamate is simultaneously removed from cell (7). A decrease in CySS causes a lower level of Cys plasma concentration which helps reduce oxidant activity (apoptosis) and decreases adhesion of monocytes to other cells (7). Zinc intake seems to be beneficial in the reduction of oxidizing activity through its action on CySS, proving to be potentially beneficial in the delay and development of AMD (7).

Discussion and Conclusion

Age Related Macular Degeneration is a serious problem in the United States. Recent research has been done on the possible benefits of antioxidants and zinc as preventative treatments. The theory is that oxidation damage to the retina can be prevented by the presence of antioxidants; vitamin A, vitamin E, β-carotene, zinc, lutein, and zeaxanthin, and increasing supplements of these nutrients or increasing dietary intakes will help avoid AMD. However, study results have been inconclusive. Some show benefits from slightly high doses of supplements, while others have shown no benefits from supplementation. One belief is that the supplementation dose was not large enough for any significant results to be discovered. In some trials the length of the experiment was not long enough to cause a beneficial change in patients. Overall, more research is needed. Future studies should probably be done for longer periods of time and may need to include larger daily intakes of these supplements.

Recommendations and Dietetic Applications in Practice

Since no significant benefit can be concluded from the current research, it is not possible to make specific recommendations for taking specific nutrients. However, we do know that increased consumption of fruits and vegetables, which are good sources of these nutrients, can be beneficial for preventing other serious illnesses such as obesity, cardiovascular disease, and cancer. Until we know more about supplementation, the best advice is to encourage an increased intake of fruits and vegetables which appear to be protective in AMD.

References:

1. Nation Eye Institute. Age-Related Macular Degeneration. Available at: http://www.nei.nih.gov/health/maculardegen/armd_facts.asp. Accessed February 21, 2009.
2. Gropper SS, Smith JL, Groff JL. *Advanced Nutrition and Human Metabolism.* 5th ed. Belmont, CA: Wadsworth; 2009: 314-496.
3. Cho E, Stampfer MJ, Seddon JM, Hung S, Spiegelman D, Rimm, EB, Willett WC, Hankinson SE. Prospective Study of Zinc Intake and the Risk of Age-Related Macular Degeneration. *Annals of Epidemiology*. 2001;11(5):328-336.
4. Bartlett HE, Eperjesi F. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial. *European Journal of Clinical Nutrition*. 2007;61:1121-1127.
5. Christen WG, Manson JE, Glynn RJ, Gaziano M, Chew EY, Buring JE, Hennekens CH. Beta-carotene and Age-related Maculopahty in a Randomized Trial of U.S. Physicians. *Arch Ophthalmol*. 2007;125(3):333-339.
6. Cangemi FE. TOZAL: An open case control study of an oral antioxidant and omega-3 supplement for dry AMD. *BMC Ophthalmol*. 2007;7:3.
7. Sternberg P, Ha K-N, Moriarty-Craige SE, Lynn M, Bressler S, Gensler G, Jones DP. Effects of Long-term Zinc Supplementation on Plasma Thiol Metabolites and Redox Status in Patients with Age-related Macular Degeneration. *Am J Ophthalmol.* 2007;143(2):206-211.