Introduction

Age-Related Macular Degeneration (AMD) is the leading cause of irreversible blindness in the elderly. Because no treatment for the disease currently exists, the focus of research endeavors has been the primary prevention of disease occurrence.

Although the exact cause of AMD is unknown, research suggests that there are a number of risk factors: Age. It is estimated that four to ten million Americans between age 45 and 75 years suffer from AMD. Race (higher in Caucasians), sex (higher and females), smoking, hypertension, cardiovascular disease, family history, high serum cholesterol, body mass index (kg weight / height2 m2), plasma fibrinogen level, and nutritional and antioxidant status have also been demonstrated to be associated with AMD (1,2).

However, other than age, sex and smoking these risk factors have not been consistently demonstrated across different studies. We will focus here on the subject of nutritional and antioxidant status and the potential role of supplementation on the progression of AMD.

The macula is a region of the retina that is responsible for exquisite visual acuity as well as color vision. Therefore most of the photoreceptors in the macula are cones. In the center of the macula is a depression or fovea that contains a 1:1 relationship between the cone photoreceptor and its retinal ganglion cell, the first neuron of the visual tract. Generally, neurons and even retinal ganglion cells in the rest of the retina receive input from many photoreceptors. Thus the 1:1 relationship in the fovea accounts for the visual acuity in this area (3).

There are two distinct forms of AMD: nonexudative (dry) and exudative (wet) which both tend to be progressive and bilateral though they differ in presentation, management and prognosis. Exudative AMD is the more severe of the two and it accounts for 90% of all cases of legal blindness due to AMD. The dry form demonstrates varying degrees of atrophy and degeneration of 3 centrally concentric tissue layers in the eye: the retina, the retinal pigment epithelium (RPE, which nourishes the retina), and Bruch's membrane (which is the basement membrane of the RPE) (3).

The most prominent clinical feature is the appearance of drusen, yello-white deposits that collect between the Bruch's membrane and the RPE. Patients with the dry rarely have significant loss of vision. However, the exudative (wet) form tends to develop suddenly. Patients who experience significant loss of vision demonstrate neovascularization (blood vessel proliferation) just below the retina. In addition, collections of serous fluid in between Bruch's membrane and the RPE cause detachment from the inner surface of the eye. When either of these processes, wet or dry, implicate the region of the macula, a detachment will lead to irreversible loss of central vision termed macular degeneration (3).

Macular pigment, omega-3 fatty acid, and antioxidant vitamins

Many studies have shown associations between certain vitamins, antioxidants in particular, and incidence of AMD. Currently, there is no conclusive diagnostic test that predicts the incidence or progression of AMD. However, based on the underlying physiology and biochemistry, researchers hypothesize and then attempt to test, or at least approximate, how specific compounds might be important in the normal function of the macula and by extension the pathophysiological processes that mediate its degeneration.

One school of thought suggests that because the retina is prone to oxidative damage caused by ionizing radiation in sunlight, known antioxidants like Vitamin E, carotenoids, and vitamin C would tend to have a protective effect against oxidative damage and reduce the incidence of AMD. Epidemiological data suggest that individuals with low blood plasma concentrations of carotenoids and antioxidant vitamins are at increased risk of developing AMD. Primate studies have also demonstrated that regions of the monkey retina that have low concentrations of these compounds correspond with the location of early signs of AMD in humans (4).

Klein et al. (1994) hypothesized that melanin in the eye, acting as a free radical scavenger might protect the macula from oxidative damage that leads to macular degeneration. Further, in individuals with higher pigmentation the incidence of AMD should be lower. To test this hypothesis, Klein et al. (1994) retrospectively analyzed the population set of subjects that participated in the Third National Health and Nutrition Examination Survey (NHANES III). In particular, they analyzed the prevalence of AMD in 3 different racial/ethnic groups: non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. The prevalence of AMD in the noninstitutionalized civilian United States population age 40 and older, as estimated by the sample, is 9.2%. Results demonstrated a higher prevalence (9.3%) in non-Hispanic whites and lower prevalence (7.4%, 7.1%) for non-Hispanic blacks and Mexican Americans, respectively. One plausible conclusion from this study is that pigmentation indeed provides a protective affect which reduces the overall risk of AMD.

Hammond et al. (1996) tried to address why the incidence of AMD is higher in females than males. They selected macular pigment (MP) which is composed of the lipid soluble xanthophylls, Lutein (L) and Zeanthine (Z) (which are highly concentrated in the macula) as an indicator of macular health. Previous studies have determined that large differences in macular pigment density exist among individuals. Hammond et al. (1996) determined that this difference might be due to sex. Results showed that males had a 38% higher macular pigment density compared to females for a given dietary intake and circulating plasma levels. These data suggest one reasonable explanation for the higher incidence of AMD in women compared to men (6).

Hammond et al. (1997) hypothesized that if macular pigment density could be increased through dietary modification, supplementation of L and Z might reduce the incidence of AMD over time. Results of a 15 week prospective dietary modification that included 60g spinach (L=10.8mg, Z=0.3mg) and 150g corn (L=0.4mg, Z=0.3mg) demonstrated an increase (19%) in macular pigment density that was sustained over several months post-intervention (7).

Another school of thought concerns the possible role of omega-3 polyunsaturated fatty acids in the retina in reducing the incidence of AMD. It is known that the retina concentrates omega-3 polyunsaturated fatty acids in higher quantities than other tissues, specifically docosahexaenoic acid (2). Polyunsaturated fatty acids have previously been shown to reduce the risk of atherosclerosis by unknown mechanisms. Physiologically, a protective effect of omega-3 fatty acids is also plausible in the retina as they may be important in the maintanence and renewal of cell membrane and other retinal compounds following oxidative damage (2).

Smith et al. (2000) studied how dietary intake of food rich in omega-3 polyunsaturated fatty acids, namely fish, might impact the incidence of AMD. Results demonstrated a 50% reduction in the incidence of AMD (n=3000) in the subgroup that consumed fresh or frozen fish 1-3 times per month compared to <1 time per month. Importantly the results showed that the protective

effect of omega-3 fatty acids reaches a threshold beyond which no additional protective effect is seen. This result is consistent with previous findings that vitamin E antioxidant status is compromised by the consumption of high-fish diets (2).

In addition to macular pigment density and omega-3 polyunsaturated fatty acids , a third focal point that has received great attention revolves around the potential role of antioxidant vitamins including vitamins E and C, beta-carotene, and others.

Recently, the Physicians Health Study I, a long term (began 1982), randomized, double-blind, placebo-controlled trial in healthy male physicians (n=22,071) demonstrated that supplementation of beta-carotene and other antioxidants showed no significant effect, positive or negative, on the incidence of cancer and coronary vascular disease (8). Christen et al. (1999) examined this same cohort and asked whether self-selection for supplementation with antioxidant vitamins affected the incidence of AMD. The results of their analysis demonstrated statistically non-significant reductions (13%, 10%) in the risk of AMD with vitamin E and multivitamin supplementation respectively. By contrast, supplementation with vitamin C alone showed a relative risk increase of 0.03% (also not statistically significant). Overall, results remain inconclusive and suggest that large reductions in risk of AMD due to antioxidant supplementation are unlikely (8). Currently, studies are underway that hope to report on the reasonable existence of smaller, incremental reductions in risk.

Discussion

As more and more data becomes available it becomes important to re-examine the sample populations that have been studied and continue to be studied. The risk of sampling error and other methodological flaws haunts most clinical research studies and at least one explanation of the disparate results that have been attained over the last two decades has been offered. With regard to cancer, the Physicians Health Study I demonstrated that in well-nourished, healthy populations, supplementation of beta-carotene had insignificant effects on the overall incidence of cancer (9). However, in a population of physicians considered undernourished as measured by low levels of plasma beta-carotene, result showed a reduction in the risk of cancer. These results were consistent with the Chinese Cancer Prevention Study that prospectively combined treatment of Vitamin E, beta-carotene and selenium in an undernourished population (10).

In light of these findings, it has been suggested that similar reductions in AMD might be seen in undernourished populations undergoing antioxidant supplementation. However, no studies have been done to measure the increased risk of AMD in undernourished populations. One might hypothesize that for a given state of undernourishment and a corresponding risk of AMD that antioxidant supplementation would revert the risk of the sample population to that of the overall population. Furthermore, it is uncertain whether any risk reduction in the undernourished population following supplementation would be statistically significant from the undernourished state.

In addition, because no predictive or diagnostic tests exist for AMD, important methodological questions arise when investigators select variables that can be measured to use as indicators of risk or progression of disease. Two commonly used variables are circulating plasma levels and dietary intake of specific factors known to have physiological role in the macula. However, this

measurement begs the question of how closely plasma concentration, for example, approximates physiological function, or as the case may be, dysfunction (11). The fact of the matter is that current research, to a great extent, relies on drawing conclusions from data that is itself based on assumptions.

As a result of preliminary findings that suggest antioxidant vitamins may play a role in AMD, the media and private businesses have created a flurry of dietary supplementation with antioxidants by consumers (1). Physicians, as well, have contributed to the increase in supplementation not so much by endorsing their use but by suggesting that antioxidant supplementation probably can not hurt or make the situation any worse.

However, to date, no large-scale, randomized trials concerning the effects of dietary supplementation of antioxidant vitamins on eye disease namely cataract and AMD have been completed. Therefore it is extremely premature for any recommendations to the effect to be made.

In a related field, research into the incidence of lung cancer in smokers and antioxidant supplementation demonstrates additional cause for concern surrounding the use of such vitamins in the general population. To date, two major studies of antioxidant supplementation on the incidence of lung cancer in current smokers have shown marked increases. The Alpha-Tocopherol Beta Carotene (ABTC) lung cancer prevention study (1994) demonstrated a statistically significant (18%) increase in the occurrence of lung cancer (n=29,000 male smokers) in subjects taking 20mg of beta-carotene per day. In 1996, the New England Journal of Medicine, published results from the Beta Carotene and Retinol Efficacy Trial (CARET) that showed a statistically significant increase (28%) in the incidence of lung cancer in current or past heavy smokers (n=14,254 men and women).

Results from these two studies strongly suggest that widespread use of antioxidant supplements in the general population for the purpose of reducing risk of AMD might not only prove inefficacious but might lead to premature death from early incidence of lung cancer. It is highly possible that in smoking patients antioxidants might cause adverse effects that outweigh hypothesized benefits. In addition, however, because conclusive evidence to the contrary does not yet exist physicians should exercise strong caution in condoning antioxidant supplementation for the prevention of AMD in the general patient population. The latest research suggests that physicians should only consider raising the intake of antioxidants in patients who are undernourished (9). Importantly, in these patients, caution should be taken to avoid supplementing beyond the recommended dietary allowance (RDA). In these patients it is probably advisable to focus on restoring proper dietary nutrition through natural food sources and to reserve exogenous supplementation for cases where the latter is not achievable. Further trials should be done to ascertain a Tolerable Upper Intake Level (UL) component of the Dietary Reference Intake (DRI) system.

Currently there are several important studies underway of the appropriate design and magnitude from which it is hoped that more conclusive data can be drawn with regard to AMD and nutritional supplementation. The Physician's Health Study II, a study of 15,000 physicians is being coordinated by the Department of Medicine at Brigham and Women's Hospital in Boston to assess the results of beta-carotene, Vitamin E and C and multivitamins on the prevention of AMD among other major diseases. In addition, the Age-Related Eye Disease Study (AREDS) is

an ongoing clinical trial of high dose vitamin and mineral supplements and the incidence of AMD. This study was initiated primarily because there is widespread use of supplements at pharmacological doses for the treatment and prevention of AMD despite the absence of comprehensive studies that define efficacy let alone safety. As well there are at least two other major prospective clinical trials underway to study the role of vitamin and mineral supplement in the disease process of AMD: the Women's Health Study (WHS), and the Women's Antioxidant Cardiovascular Study (WACS).

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