Introduction

Age related macular degeneration (AMD) is the leading cause of irreversible vision loss in the elderly populations of the US and Western World (1). It is estimated that 30% of the over-75-year-old age group is affected (2) and as longevity increases, the prevalence of AMD and socioeconomic impact of this condition will continue to rise. Although the pathogenesis of AMD is still being debated, studies about the causative effects between oxidative damage and AMD are mounting (3). This has led to research regarding the antioxidant and light absorptive qualities of the dietary carotenoids, lutein and zeaxanthin, and their possible protective role against AMD. This paper will review the current literature on the protective role these carotenoids might play against the progression of AMD.

Macular Pigment

Lutein and zeaxanthin are collectively referred to as macular pigment (MP) because they are the primary carotenoids in the human macula and retina (2). Compared to the roughly fifty other carotenoids in the human diet, MP's are deposited five times higher in the macula region, where visual acuity is best (1). This macular pigment is known to be positioned between incoming light and the photo receptor outer surface (4) but its exact function has not yet been proven. Hypothesis' include macular pigments absorption of blue light which has otherwise photo-damaging oxidative effects, the decrease in light scatter to aid visual performance, and anti-oxidants effects against harmful chemicals (1, 2, 5).

Dietary Sources

Along with B-carotene, which is also in the carotenoid family, MP's are found in yellow, red, and green fruits and vegetables (6). Of the two, lutein is found much more commonly than zeaxanthin, which has sources mainly limited to greens, orange fruits like nectarines and oranges and squash (2). The highest overall density of both macular pigments however, is found in egg yolk and maize (2). Overall, dietary carotenoid levels can be increased by eating a well-balanced diet with an emphasis on fruits and green-leafy vegetables.

Interestingly, it has recently been found that the dried fruit of Lycium barbarum, which traditionally has been prescribed by Chinese herbalists for many eye diseases, contains a high amount of zeaxanthin (2).

Epidemiological Evidence

There are several epidemiological studies indicating a role for dietary macular pigment in protection against age related macular degeneration.

A study published in 1993 looked at the dietary intake of MP in 356 patients recently diagnosed with AMD vs. 520 control subjects from the same geographic area matched for age and sex (7). Adjusting for other known AMD risk factors, it was found that those in the highest subgroup of carotenoid intake had a 43% lower risk for AMD compared with those in the lowest.

A similar study published in JAMA comparing serum levels of carotenoids, vitamins C and E, and selenium in 421 patients with age-related macular degeneration and 615 controls found the adjusted risk for having ARM was cut in half by the patients with higher serum levels of carotenoids vs. those in the lower serum level group (8).

But, both of these studies have weaknesses in the fact that it is nearly impossible to control for co-existing factors in case-control structured studies. For example, other factors such as lifestyle, overall diet and additional unknown risk factors that have associations with higher serum carotenoid levels and AMD might create a misleading link between carotenoids and a lower risk of having AMD.

Further, a case-control study of 334 total patients published in the Archives of Ophthalmology in 1995 found evidence conflicting with the results of the first two studies. The study looking at serum carotenoids and age-related macular degeneration found that serum levels of carotenoids were similar in patients with AMD and in the control group (9). This evidence contrarily suggests there is not a link between serum levels of carotenoids and risk for acquiring AMD.

Experimental Evidence

It has been proven that lower levels of MP in the retina are present in AMD (10). Animal models that test the ability of dietary carotenoids to increase MP density in the retina have shown reasonable success.

A controlled study feeding the carotenoid containing Chinese herbal extract, Lycium barbarum mentioned above, to rhesus monkeys while looking at changes in serum and tissue levels of lutein and zeaxanthin found that serum levels of these carotenoids were significantly increased with supplementation (11). A recent 2004 study by the same author reproduced these results by feeding 18 monkeys carotenoid free diets from birth and switching six to carotenoid containing diets in later life (12). Autopsy results on both groups showed that retinal epithelium in the carotenoid free monkeys had a significant decrease in retinal cell density compared to that of the monkeys switched to a carotenoid containing diet. This study suggests that low retinal MP density can be reversed in later life.

Nutritional studies relating low MP levels and *early* retinal degeneration in animals have also been presented. A study with 48 macaque monkeys raised one group on a completely MP free diet and a control on a standard laboratory diet. The maculae in the MP free monkeys soon disappear after birth and retinal abnormalities signifying early AMD become apparent (13).

Evidence of low dietary intake of MP linked to early signs of AMD in humans however, has not been presented (2).

Clinical Evidence

Many study approaches have been devised to test the hypothesis that MP density is protective against AMD in humans. An autopsy study published in 2001, looked at

macular dissections of 56 deceased patients with AMD and 56 without (10). MP density in all macular regions was less in the AMD donors than for the controls. The authors of the study showed that the overall results indicated an inverse relationship between MP density in the retina and risk for AMD. A causative role between these two factors though, was not definitively proven.

In another study, dietary supplementation with carotenoids by spinach and sweetcorn intake was given to 13 participants for 15 weeks (14). Serum and retinal MP levels were measured at set points and three response groups resulted. Eight participants had increases in both serum and retinal levels. Two had a serum but not retinal response, and one showed neither response. The remaining two subjects were given sweetcorn only (just zeaxanthin), and one showed a significant rise in MP density, while the other did not. The study's weakness was its size but, it suggests that dietary intake of carotenoids from vegetables can effectively increase MP retinal density.

The LAST study (Lutein Antioxidant Supplementation Trial) published in 2004, was a randomized, double-masked placebo controlled trial looking at 90 patients with AMD for a 12 month period. One patient set received lutein supplementation while the other received placebo (1). The AMD patients receiving lutein showed increased optical pigment density and Snellen visual acuity was increased by an average of 5.4 chart letters. Patients receiving placebo showed no significant change in any of the measured parameters (1). This is an important clinical study because along with correlating dietary intake of carotenoids with higher MP retinal density, the study showed a measured clinical improvement in vision.

A recent study published in 2004, tested the hypothesis that AMD sufferers have an abnormal gastrointestinal absorption or decreased deposition of MP into the retina (15). The study tracked plasma lutein and retinal MP levels with lutein supplementation among a group with AMD and one without. The study showed that MP retinal density and serum levels rose almost identically in both groups providing the first clinical evidence that healthy elderly subjects and sufferers of AMD do not malabsorb lutein.

Conclusions and Further Research

To date, there is a large body of evidence suggesting the macular pigments lutein and zeaxanthin play a protective role in the progression of age-related macular degeneration. However, definitive evidence from larger randomly controlled trials is lacking.

Fortunately, the high interest and many emerging clinical trials on this subject will help drive further research and understanding. To these ends, the Age-Related Eye Disease Study (AREDS) through the National Institute of Health is currently following two large cohorts of patients with AMD, one with MP supplementation and one with placebo (2). The results of this and other studies will give us more critical information necessary to develop possible therapeutic strategies for combating AMD in the future.

As for supplementation there is no current agreement among scientists and doctors on its clear benefit. With regimental dosage data lacking as well, one should use ocular vitamin

supplements with caution. The best recommendation for patients with AMD or the risk of disease might be learning further about dietary sources rich in these carotenoids and using this information to eat a well balanced diet high in fruits and vegetables.

While nature may not have provided us with a “cure-all” solution for age-related macular degeneration just yet, the data certainly suggests there are steps we can take to reduce our risk.

Works Cited:

1. Richer S, Stiles W, Statkute L, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study. Optometry 2004;75:216-30

2. Mozaffarieh M, Sacu S, Wedrich A. The role of the carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: A review based on controversial evidence. Nutr J. 2003; 2: 20.

3. De La Paz MA, Anderson RE. Regional and age-dependent variation in susceptibility of the human retina to lipid peroxidation. Invest Ophthalmol Vis Sci 1992;33:3497–9.

4. Snodderly DM, Auran JD, Delori F, et al. The macular pigment. II. Spatial distribution In primate retinas. Invest Ophthalmol. Vis Sci 1984;25:674-85

5. Snodderly DM. Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins. Am J Clin Nutr 1995;62:1448s–60s.

6. Blodi BA. Nutritional Supplements in the Prevention of Age-Related Macular Degeneration. Insight. Jan-Mar. 2004:29(1); 15-16.

7. The Eye-Disease Case Control Study, Group. Antioxidant status and neovascular age-related macular degeneration. Arch Ophthalmol 1993;111:104–109.

8. Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, et al. Dietary carotenoids, vitamin A, C, and E, and advanced age-related macular degeneration. JAMA 1994;272:1413–1420.

9. Mares-Perlman JA, Brady WE, Klein R, Klein BE, Bowen P, Stacewicz-Sapuntzakis M, et al. Serum antioxidants and age-related macular degeneration in a population-based case control study. Arch Ophthalmol 1995;113:1518–1523.

10. Bone RA, Landrum JT, Mayne ST, Gomez CM, Tibor SE, Tweiska EE. Macular pigment in donor eyes with and without AMD: a case-control study. Invest Ophthalmol Vis Sci 2001;42:235–240.

11. Leung IYF, Tso MOM, Li WWY, Lam TT. Absorption and tissue distribution of zeaxanthin and lutein in rhesus monkeys after taking fructus lycii (Gou Qi Zi) extract. 2001;**42**:466–471.

12. Leung IY, Sandstrom MM, Zucker CL. Nutritional manipulation of primate retinas, II: effects of age, n-3 fatty acids, lutein, and zeaxanthin on retinal pigment epithelium. Invest Ophthalmol Vis Sci. 2004 Sep;45(9):3244-56.

13. Malinow MR, Feeney-Burns L, Peterson LH. Diet-related macular anomalies in monkeys. Invest Ophthalmol Vis Sci. 1980 Aug;19(8):857-63.

14. Hammond, Br, Jr; Johnson, EJ.; Russel, RM.; Krinsky, NI.; Yeum, KJ.; Edwards, RB., et al. Dietary modification of human macular pigment density. Invest Ophthalmol Vis Sci 1997;38:1795–1801.

15. Koh HH, Murray IJ, Nolan D, et al. Plasma and macular responses to lutein supplement in subjects with and without age-related maculopathy: a pilot study. Exp Eye Res. 2004 Jul;79(1):21-7.