Brief Critical Review

Dietary Lutein and Zeaxanthin: Possible Effects on Visual Function

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Of the many carotenoids circulating in human sera, only lutein and zeaxanthin are accumulated throughout the tissues of the eye. Within the eye, they reach their highest concentration in the central retina, where they are clinically referred to as the macula lutea. Lutein and zeaxanthin, more commonly referred to as macular pigments, may serve a variety of roles in the specialized vision of higher primates. This paper reviews recent studies investigating the influence of macular pigments on human visual performance. Such studies have offered insight into why lutein and zeaxanthin are uniquely concentrated in ocular tissues.

Introduction

Visual loss is a common problem in older individuals. This is largely due to the fact that the eye contains numerous structures that, unlike other bodily tissues, do not undergo processes of biological renewal. For example, the anterior portion of the eye is composed of clear optical lenses (the cornea and crystalline lens) that focus light onto the retina (the neural tissue that lines the back of the eye; see Figure 1). Most of the cells within the lens are formed during embryonic development and are never replaced. Thus, damage to the lens (usually in the form of oxidative modification of proteins) simply accumulates with age and eventually results in the development of cataracts (the leading cause of blindness in most of the world). The retina is neural tissue and therefore contains cells that do not undergo mitosis. Loss of these cells is therefore permanent, leading to degeneration of the retina and the continuing deleterious accumulation of metabolic debris. Ultimately, the age-related changes that occur in the lens and retina lead to substantial visual loss for many older Americans. Such changes to the retina, in their most exacerbated form, can lead to an irreversible form of blindness called age-related macular degeneration (AMD). A recent large meta-analysis estimated an overall prevalence of advanced AMD of 1.47% (about 1.75 million Americans), making it the most common form of blindness in developed countries (this number is expected to double by 2020). The Eye Diseases Prevalence Research Group concluded that “a determined effort to identify effective preventive strategies will be needed if we are to avoid a large increase in the numbers of persons having this condition.”

One of the more promising preventive strategies currently under investigation is dietary modification. Recently, a large NIH-sponsored intervention (the Age-Related Eye Disease study or AREDS) found that 25% of those with early signs of AMD did not develop severe AMD and vision loss (over the five-year span of the study) when supplementing with the nutrients zinc, beta-carotene, and vitamins C and E. By extension, one could predict that if the AREDS formulation was given to the Eye Disease Study Group subjects (7.3 million of which showed early signs of AMD risk), about 1.8 million of those patients would not develop AMD and/or severe vision loss over a five-year period. Our more current understanding of the relationship between diet and AMD risk suggests that we could improve the AREDS formulation to increase these effects even more. For example, the AREDS cocktail did not include the dietary carotenoids lutein and zeaxanthin, and increasing evidence suggests that these specific carotenoids may be particularly effective at both preventing AMD and ameliorating visual losses that tend to accompany both aging and AMD.
Diet and Risk of Age-Related Eye Disease

Ocular tissues accumulate high concentrations of many different types of nutrients. Unless this accumulation is purely incidental, these nutrients must serve some function within the tissue. The function of many nutrients within the eye has been well characterized (e.g., the role of vitamin A as a component of visual photopigment). There are other instances, however, where the function of ocular nutrients has been less well defined. This is perhaps most true for studies examining the question of whether diet serves to protect ocular tissues from damage that accrues with age.

Long-term dietary intake is notoriously difficult to quantify. Moreover, chronic disease is multifactorial (including non-dietary factors such as genetic predispositions) and tends to develop slowly over a long time course (i.e., a lifetime). Thus, epidemiology is often faced with the challenge of quantifying small effects over long time periods. Such effects, however, can be quite meaningful. For example, imagine that, all things being equal, high dietary intake of vitamin C reduced oxidative stress to the retina by 1%. Such a small effect would be difficult to quantify and could be statistically non-significant even when using large sample sizes studied for only a relatively short period. Even this small of an effect, however, aggregated over many years could be clinically meaningful.

Notwithstanding these difficulties, a large number of epidemiological studies support the notion that dietary factors are strongly related to the development of age-related eye diseases such as macular degeneration and cataract. Such results are often explained based on models of oxidative stress. The idea that oxidative stress could be a particularly important etiological factor in the development of degenerative eye disease is supported by a large and diverse set of studies. The oxidative model is particularly interesting due to its potential modifiability: if oxidative stress is lowered, the probability that an individual will develop eye disease is also lowered. For example, smoking has consistently been identified as a behavioral risk factor for AMD. Smoking increases oxidative stress to the retina and, consequently, by discontinuing smoking, oxidative stress to the retina is decreased and the probability that an individual will develop AMD may be decreased as well. Similarly, diet could either reduce (e.g., by being rich in antioxidants) or increase (e.g., by being rich in saturated fats) oxidative stress to the retina. Thus, theoretically, an improved diet could also decrease the risk of eye disease.

Nutritional Intervention and Visual Performance

For the aforementioned reasons, diet is often seen as a means of preventing age-related eye disease. At first glance, focusing on prevention makes perfect sense. As noted, photoreceptors are neural cells that do not undergo mitosis and thus, once lost, cannot be restored. There are reasons, however, to believe that even late-stage dietary intervention could influence the progression of retinal disease. For example, oxidative damage requires the presence of a photosensitizer. One of the more significant photosensitizers for the retina is lipofuscin, which accumulates with age and is highest in the elderly. This accumulation may make this group the most susceptible to light-initiated oxidative damage.

A related possibility is that diet could treat many of the symptoms of eye disease, which manifest as a loss of visual function. For example, Hammond et al. found that ocular levels of the dietary carotenoids lutein and
zeaxanthin were strongly related to lens optical density as a function of age. Specifically, subjects with higher levels of ocular lutein and zeaxanthin tended to have lower lens optical densities, which results in increased light reaching the retina and, presumably, better visual function. In another study, Hammond et al.\textsuperscript{17} found that older subjects with relatively high retinal concentrations of lutein and zeaxanthin (macular pigments; see the right side of Figure 1) had higher scotopic (“nighttime” vision), photopic (“daytime” vision), and short-wavelength (blue) sensitive cone sensitivity compared with those with lower levels of macular pigment. Thus, higher levels of ocular lutein and zeaxanthin may lead to increased lenticular transmission and higher retinal sensitivity in normal elderly subjects.

Recently, Hammond et al.\textsuperscript{18} found that subjects with higher macular pigment density also had higher critical flicker fusion thresholds (a measure of temporal vision or processing speed that is often considered to be a good general measure of visual health). The possibility that lutein and zeaxanthin could improve visual performance has also been found when studying patient populations. For example, Olmedilla et al.\textsuperscript{19} supplemented cataract patients with 15 mg of lutein three times a week for up to two years, and found that the lutein-supplemented patients’ visual acuity improved nearly one line on the Snellen visual acuity chart compared with the placebo controls. Similarly, Richer et al.\textsuperscript{20} recently found that after 12 months of 10 mg of lutein or 10 mg of lutein plus antioxidant supplementation, visual acuity in AMD patients improved by 5.4 and 3.5 letters, respectively, on the Snellen chart. Those receiving a placebo showed no improvement in acuity.

**Mechanisms of Action**

If it is true that increasing macular pigment improves the visual performance of patients and normal subjects, determining what mechanism is responsible for such an improvement is imperative. There are two possibilities, one based on optical filtering and the other based on changes in the underlying biology. With regard to the latter, a number of mechanisms (in addition to the obvious improvements related to simply having a more healthy retina) are possible. For example, in model systems,\textsuperscript{21} lutein can improve gap junction communication. Increasing lutein and zeaxanthin intake could therefore improve signaling efficiency throughout the visual system (a possibility consistent with the finding that macular pigment is positively related to CFF values\textsuperscript{18}). Age-related declines in neuronal signal transduction have been reversed with dietary supplementation of carotenoid-rich foods (e.g., spinach) in rat models.\textsuperscript{22}

In addition to purely biological and/or protective effects, macular pigment could improve visual efficiency through a variety of optical mechanisms. This concept was originally proposed over a century ago in 1866 by Max Schultze\textsuperscript{23} and then again by the Nobel laureate George Wald in 1949,\textsuperscript{24} as well as by many others. These researchers suggested that macular pigment could improve visual acuity by reducing longitudinal and lateral chromatic aberrations. Chromatic aberrations can potentially degrade a retinal image because not all wavelengths are perfectly focused on the retina. For example, when objects are viewed at a distance, only mid-wave (i.e., green) light is focused on the retina. Short-wave light (that appears blue) and long-wave light (that appears red) are focused significantly in front of and behind the retina, respectively.\textsuperscript{25} This means that, based purely on the optics of the eye, objects viewed in daylight should be surrounded by bluish fringes. The fact that they are not means that the human visual system has some means of correcting for these optical aberrations. One possibility is that, as a yellow filter that lies in front of the photoreceptors,\textsuperscript{26} macular pigment prevents degradation of the retinal image by absorbing badly focused short-wave light. Reading and Weale\textsuperscript{27} demonstrated that macular pigment had the optimal spectral characteristics to serve this function. Yoon and Williams\textsuperscript{28} have shown that chromatic aberration, especially at shorter wavelengths, does indeed degrade acuity and contrast sensitivity. Despite these theoretical arguments, however, no one has yet measured macular pigment and acuity (under the correct conditions) to confirm whether macular pigment actually serves this function.

There is some basis for questioning whether macular pigment does improve acuity in this manner. McLellan et al.\textsuperscript{29} for instance, argued that the effects of longitudinal chromatic aberrations are reduced due to counterbalancing from wavefront aberrations, making macular pigment unnecessary. Their result, however, does not apply to pupils 2.5 mm or smaller or to stimuli at higher luminances (the authors used relatively low luminance values). Therefore, for daylight vision, in which pupils are constricted to approximately 2 mm, the results of McLellan et al. may not apply. Nonetheless, their data emphasize the point that this question must be addressed by empirical study.

In addition to blur arising from within the eye, visual degradation also occurs due to external optical sources. It may not be a coincidence that the peak absorbance of macular pigment is 460 nm, which is also the peak wavelength of sky light. Of course, the reason that the sky appears blue is that the more highly energetic short-wave component of white sunlight is more easily scattered by particles in the atmosphere (e.g., oxygen and nitrogen, termed Rayleigh scatter). In addition, haze aerosols, which are composed primarily of dust, volcanic ash, pollution particles, sea salt, and exudates from
With regard to macular pigment level, subjects with more foliage, more easily scatter short-wave light. Wooten and Hammond\textsuperscript{30} originally proposed that this preponderance of short-wave light in the atmosphere results in a bluish veiling luminance that degrades visibility, i.e., how well and how far we can see targets in the outdoors. Macular pigment may improve vision through the atmosphere by preferentially absorbing the short-wave energy produced by blue haze and, thereby, increasing both the contrast within the objects that we view and the contrast of those objects with respect to their backgrounds.

Empirical models derived by Wooten and Hammond\textsuperscript{30} suggest that this effect could be very meaningful. For example, when viewing a series of parallel ridges covered with vegetation, ridges nearby will appear green. With each successive ridge, however, air light reduces contrast, until distant ridges are lost in a milky bluish haze, even on a clear day (e.g., in the Green River area in Wyoming, the average visual range in June is 108 miles). The visibility hypothesis predicts that an individual with high macular pigment would be able to distinguish such ridges up to 27 miles farther than individuals with little or no macular pigment but equal Snellen acuity. Although intriguing, it is important to emphasize that, like the acuity hypothesis, the visibility hypothesis has not yet been empirically validated.

Another explanation for how lutein and zeaxanthin could improve visual performance is by limiting problems due to glare. A major complaint in many AMD patients is visual discomfort as a result of exposure to even moderate lighting.\textsuperscript{31} This is termed “photophobia” or “discomfort glare” and refers to discomfort, or in extreme cases, pain on exposure to sufficiently intense light. Whereas for clinical populations there exist only anecdotal data for this phenomenon, the spectral and spatial properties of visual discomfort have been well documented in normal subjects.\textsuperscript{32,33} Stringham et al.\textsuperscript{32} showed that thresholds for photophobia responses (squinting of the eyes in reaction to an intense light) were much lower for lights of short wavelengths (those in the blue region of the visible spectrum) than for lights of middle (green) or long (red) wavelengths. In other words, it took much less light energy to elicit an aversive response when the light was of a short wavelength.

Interestingly, the action spectrum for photophobia (after correction for macular pigment and ocular media absorption) was shown to approximate both the threshold retinal damage function for rhesus monkeys determined by Ham et al.\textsuperscript{34} and the action spectrum for aerobic photoreactivity of lipofuscin (thought to act as a photosensitizer for the generation of reactive oxygen species in the retina).\textsuperscript{15} It appears, therefore, that photophobia is a behavioral mechanism that is biased to protect biological tissue from potentially damaging short-wavelength light. With regard to macular pigment level, subjects with higher levels of macular pigment were shown to tolerate more short-wavelength light energy before the photophobia threshold was reached. A similar result was found in another study of photophobia\textsuperscript{33} in which thresholds to a broadband white light (containing much short-wavelength energy) versus an orange light (containing no short-wavelength energy) were compared. Overall, the subjects were shown to be more sensitive to the broadband white light, but those subjects with higher levels of macular pigment were able to tolerate higher levels of that light when viewed centrally (filtered by macular pigment) compared with peripherally. Conversely, for the orange light (not filtered by macular pigment), the subjects were shown to be very similar in their photophobia sensitivity for central versus peripheral viewing conditions. From a functionality standpoint, these studies indicate that macular pigment increases the bandwidth of comfortable visual operation via its action as a passive filter. For subjects with relatively high macular pigment levels, a conservative estimate of this effect is roughly 0.5 log units (over three times the amount of broadband light energy tolerated) compared with those with very little or no macular pigment. Although clinical populations have yet to be examined, the results of these photophobia studies suggest that dietary or supplementary modification of macular pigment in patients with AMD could feasibly attenuate photophobia.

This interpretation is consistent with data from Olmedilla et al.,\textsuperscript{19} who examined the effect of two years of lutein supplementation on glare sensitivity in patients with age-related cataract. Although they didn’t measure directly the effect of the supplementation on retinal levels of lutein (i.e., macular pigment), serum levels of lutein were shown to significantly increase in those subjects taking the supplement. After the two-year supplementation period, the lutein-supplementation subjects exhibited significantly reduced glare sensitivity, whereas the placebo group’s glare sensitivity did not change. Richer et al.\textsuperscript{20} recently examined the effect of antioxidant supplementation (including lutein) on glare recovery in patients with AMD. In contrast to the aforementioned study,\textsuperscript{20} retinal concentrations of lutein (macular pigment) were measured directly in this study. Macular pigment and glare recovery were assessed at baseline, 4, 8, and 12 months. The AMD patients who received the treatment were shown to have nearly significant glare recovery improvement (coincident with macular pigment increases) as early as 4 months after baseline, compared with no significant improvement in the placebo group. These data on glare recovery were not significant, however, perhaps due to the substantial variability found in the subjects’ recovery times (ranging from 15 to 180 seconds). Ultimately, although the exist-
ing data on patients is supportive, more careful study of this important possibility is needed.

Conclusions

If everyone had a high concentration of macular pigment, the issue of its effect upon visual performance would be purely academic. We know, however, that a wide range exists in the normal population, and that individual levels are usually strongly influenced by diet. Consequently, it is possible that people with low concentrations of macular pigment might be seeing at a level less than their potential and could be suffering negative visual effects (such as discomfort glare) that could be prevented. A number of recent studies have measured the macular pigment of larger populations (n = 68035; n = 140036) and found that the average macular pigment for these groups was very low. Thus, decreases in visual performance related to macular pigment may be quite pronounced for many Americans.

We do know that supplementing lutein and zeaxanthin can increase the macular pigment of most subjects. Nonetheless, although improvements in visual function by macular pigment are plausible, with the exception of the photophobia studies (in which a small number of subjects were used), there are no empirical data yet available to properly evaluate the hypothesis. There is also no way of knowing whether improvements in visual performance following lutein supplementation are a function of improved optics or more active biological mechanisms. Of course, these effects are not mutually exclusive. Macular pigment could both improve optics and have a salubrious effect upon photoreceptor function (e.g., by increasing membrane stability). These effects could be disentangled by empirically determining whether macular pigment does in fact improve vision through optical mechanisms (such an effect can be measured by carefully controlling spectral conditions). It must also be determined whether optical effects, if they do exist, are meaningful in a real world sense.

Despite the paucity of data, the possibility that intervention with lutein and zeaxanthin may improve visual performance is being aggressively pursued by numerous pharmaceutical companies who have marketed lutein supplements designed to improve visual performance. In this case, as with many, the market has leapt ahead of the science. Empirical studies are desperately needed, are meaningful in a real world sense.

References

15. Margrain TH, Boulton M, Marshall J, Slaney DH. Do blue light filters confer protection against age-re-
tion to macular pigment optical density. Ophthalmic and Physiological Optics (in press).


