

Lutein as a Contributing Modulator of Age-related Macular Degeneration

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Abstract

Lutein is a small-molecule carotenoid that has been studied with varying degrees of interest in both general nutrition and ophthalmology. This molecule is derived from green leafy vegetables (as well as commercially available dietary supplements) and has been postulated to act as a modulator in retinal health, specifically as a factor in the prevention of macular degeneration. The available clinical data do not suggest that lutein or the carotenoid zeaxanthin have any inherent toxicity. The presence of either or both has been linked to the prevention, but not necessarily the treatment, of macular degeneration. The available information may suggest that lutein intake as an oral supplement, coupled with awareness (and where possible modulation) of certain risk factors such as elevated body weight, smoking, and a family history of AMD, taken as part of an entire personalized treatment regimen, could positively impact the development of age-related macular degeneration.

Keywords

Carotenoid, nutrition, ophthalmology, macula, lutein

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Lutein is a carotenoid whose name is derived from *luteus*, meaning 'yellow.' It is generally found in nature in green leafy vegetables and in varying concentrations in the retinal segment and macula of humans. One may take carotenoids such as lutein into the body by direct oral ingestion of vegetables or, more recently, by dietary supplements. Reduction in levels of lutein and other carotenoid has been linked in some studies to an increased risk of posterior-segment eye diseases such as age-related macular degeneration (AMD).¹

AMD is one of the leading causes of blindness in the US and other developed countries, affecting about 12 % of the population. As with glaucoma, the disease may be asymptomatic for some time. However, in the later stages, central vision is severely impaired. There is no cure and few effective treatments for AMD. Most current treatments are centered on anti-vascular endothelial growth factor (VEGF) therapy by injection of a drug or biological molecule into the posterior segment of the eye. These treatments may be effective, depending on the molecule injected, but the injection itself can be dangerous and the treatments are expensive.² The common drugs delivered in this fashion are Macugen®, Lucentis®, and Avastin®. The last two are biomolecules. Macugen is a synthetic strand of messenger RNA, the 'message' being translated into protein at the subcellular level.

Chemistry

Lutein has a molecular formula of C₄₀H₅₆O₂ and a molecular weight of 568.87 g/mol. Lutein is identified by the International Union of Pure and Applied Chemistry (IUPAC) as β,ε-carotene-3,3'-diol. It is insoluble in water and soluble in fats, with a red–orange appearance in the solid

state. Lutein is chemically unstable in acids and is susceptible to degradation by heat and light. Zeaxanthin is a positional isomer of lutein. Both molecules have been shown to protect against oxidative stress.³

Presence in Nature

Lutein and zeaxanthin are ubiquitous in nature, occurring in a variety of plant and animal species, and have been used as colorants for poultry feed. Carotenoids such as lutein are a part of the human diet, as well as the diet of other animals, when absorbed from fruits such as kiwifruit and vegetables such as kale, lettuce, and sprouts. At present, there is no minimum daily requirement for human consumption as there is for other supplements. Data suggest that the effects of lutein seem to occur at 'increased' levels compared with normal or unsupplemented levels. This will be described below.

Role in Ophthalmology

Age-related Macular Degeneration

AMD progresses over the course of a person's life and becomes more acute as the person gets older.⁴ It is one of the leading causes of visual impairment in the Western world. What is new is the realization that there are contributing factors, such as elevated body weight and smoking, that are recent developments and can lead to the condition—as well as to other conditions such as diabetes.⁵ Wet AMD is caused by the formation of new blood vessels or angiogenesis. The encroachment of blood vessels into the retinal space causes the impairment. Angiogenesis can lead to AMD or to diabetic retinopathy, both of which cause central vision loss. There is evidence that reduction in smoking, decrease in body weight, filtering sunlight by wearing sunglasses on a consistent basis, and the

addition of nutritional supplements (such as lutein) to the diet will prevent, or modify the course of, the disease.⁵

Location and Mode of Action

Lutein is primarily found in the macula of the eyes in humans and other animals. It is carried there by the blood and lymphatic systems following ingestion. The yellowish color of the macula is due to the ingestion of lutein. Lutein and zeaxanthin are postulated to function in a variety of ways. They may act as a short-wavelength light filter, a signal transduction modulator, and an element in the structure of cell membranes.⁵⁻⁸ It is important to note that humans are not capable of synthesizing lutein; it must be obtained from the diet. Sunglasses or light-filtering intraocular lenses have been postulated to be potential modulators of AMD.⁹ A study conducted in individuals working in Chesapeake Bay showed that there is a correlation between blue or viable light and the occurrence of AMD. Other evidence comes from individuals who have undergone cataract surgery.⁹ These individuals seem to be more susceptible to the effects of ultraviolet radiation than those who have not had surgery.^{10,11} The answer seems to lie in the idea that the human crystalline lens turns yellow with age, and that this tends to protect the retina from the harmful effects of ultraviolet light.¹²

Study Results

The theory that lutein and zeaxanthin can modulate AMD has been studied in humans. In France, the Pathologies oculaires liées à l'âge (POLA) study measured plasma levels of carotenoids from 900 subjects and showed a correlation with the risk of AMD.⁹ A reduction of AMD was shown with higher plasma levels of carotenoid. A study conducted in the UK showed similar results.¹³ Seddon et al. demonstrated a statistical difference between individuals who ingested higher levels of the carotenoids lutein and zeaxanthin compared to those who did not take in the carotenoids ($p < 0.01$) in terms of prevalence of AMD.⁴ Bone et al. showed that elevated levels of lutein supplement had a positive effect on macular pigment optical density (MPOD).¹⁴ Their range-finding study conducted over 140 days showed that MPOD was linearly dependent on lutein dose. The 87 subjects in the study received daily doses of 5, 10, or 20 mg of lutein or placebo. MPOD increased at a rate that was dose-dependent.

Elevated body mass seems to increase the risk of AMD. One study has calculated that obese individuals had a 1.93 odds ratio of having a higher

incidence of geographic-atrophy AMD.⁶ The study by Seddon et al. produced similar results.⁴

Snellen et al. performed a 138-patient clinical study attempting to correlate low antioxidant intake with AMD.¹⁵ The results indicated that AMD was more prevalent in volunteers who had a low antioxidant intake, especially a low lutein intake, than in volunteers who had a high lutein intake. The study corrected for exposure to contributing factors such as overexposure to sunlight, smoking, and a family history of AMD.

However, the Carotenoids in age-related eye disease study (CAREDS), which followed nearly 1,800 American women aged 50–79 for up to seven years, found that there seemed to be no statistical correlation between the amount of carotenoids taken and the risk of AMD.¹⁶

Future Use

Lutein will continue to be used as a dietary supplement. The case studies referenced in this article show no evidence that elevated lutein levels over a long period of time are toxic. Most of the evidence suggests that dietary supplementation with carotenoids coupled with lower body mass index, protection against overexposure to sunlight, and abstinence from smoking, taken as a regimen, may be key to a decreased risk of developing AMD as a person ages or has moderate to severe AMD. Thus the ingestion of lutein and other carotenoid supplements as a long-term preventive action—in concert with tackling lifestyle issues, such as an elevated body mass and smoking—may be a viable alternative to current AMD treatments. The use of injectable compounds into the posterior segment of the eye is not optimal, whether from a patient care or from a cost standpoint. However, a family history of AMD is another key variable associated with the disease, as is the case in other diseases such as cancer. A strong correlation between AMD and a family history of AMD may serve to trump the other factors, at least in some individuals. It is important to emphasize that, while studies show that lutein can play a role in modulating ocular health, the effect is enhanced when other health risk factors (elevated body weight, smoking, etc.) are taken into account and modulated. As often with complex diseases, there are a variety of negative contributing factors, such as smoking, weight gain, and genetics, which will affect quality of life as a person ages.^{17,18} Unfortunately, an individual only has control over the first two. ■

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