

The role of the carotenoids, lutein and zeaxanthin, in protecting against
age-related macular degeneration: A review based on controversial
evidence

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Abstract

Purpose: A review of the role of the carotenoids, lutein and zeaxanthin, and their function in altering the pathogenesis of age-related macular degeneration (AMD).

Methods: Medline and Embase search

Results: Carotenoids are concentrated at the macula and have an anti-oxidant role. It has been suggested that eating green leafy vegetables, rich in the carotenoids lutein and zeaxanthin, may decrease the risk for age related macular degeneration. The scientific literature on the role of vitamin and mineral supplementation is inconclusive. Dietary nutrients containing lutein and /or zeaxanthin appear to be beneficial in protecting retinal tissues .This has prompted the inclusion of these carotenoids in several commercially available ocular vitamin /mineral supplements with numerous products all claiming superiority over their competitors. Yet evidence as to the absolute benefit of supplementation is controversial, and the optimum dosage or combination of ingredients required in ameliorating the pathogenesis of macular degenerative conditions is unknown.

Conclusion: An intake of dietary supplied nutrients rich in the carotenoids, lutein and zeaxanthin, appears to be beneficial in protecting retinal tissues, but this is not proven. Until absolute scientifically sound knowledge is available we recommend for patients judged to be at risk for AMD to: alter their diet to more dark green leafy vegetables, wear UV protective lenses and a hat when outdoors, and we urge physicians to be cautious when prescribing ocular vitamin/mineral supplements. Future investigations on the role of nutrition, light exposure and genetics hold potential in finding the cause of AMD for future treatment possibilities.

Introduction

The two major carotenoids in the human macula and retina are lutein and zeaxanthin, ^{1,2} . Similar to β -carotene, these pigments are found in various coloured fruits and green leafy vegetables. Of the 40 to 50 carotenoids typically consumed in the human diet ^{3,4} , lutein and zeaxanthin, are deposited at an up to 5 fold higher content in the macular region of the retina ¹ as compared to the peripheral retina. Zeaxanthin is preferentially accumulated in the foveal region ^{2,5} , whereas lutein is abundant in the perifoveal region. These pigments are collectively referred to as the macular pigment (MP). Although the role of the macular pigment remains uncertain, several functions have been hypothesised and these include limitation of the damaging photo-oxidative effects of blue light through its absorption ^{6,7,8} , reduction of the effects of light scatter and chromatic aberration on visual performance, ^{9,10} , and protection against the adverse effects of photochemical reactions because of the antioxidant properties of the carotenoids ^{5,11,12} .

Age related macular degeneration (AMD) is the leading cause of visual loss in people over the age of 65 in the Western world. Although the aetiopathogenesis of AMD remains a matter of debate, there is a growing body of evidence to indicate that oxidative damage plays a role ^{13,14} . Consequently, the possibility that the absorption characteristics and antioxidant properties of macular pigment confer protection against age-related macular degeneration has been postulated ^{12,15} and it has further been hypothesised that dietary supplementation with lutein and / or zeaxanthin might protect the retina and / or delay the progression of age-related macular degeneration ^{12,16,17,18} . Supplementation with foods ^{19,20,21} or supplements rich in lutein or zeaxanthin has been reported to increase macular pigment density in most, but not all, human subjects ^{19,21,22} . Yet despite the possible importance of these carotenoids in modulating the course of age-related macular degeneration, critical evidence of beneficial effect has not been found, and the role that these carotenoid supplements play in patients with age-related macular

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degeneration, or those at risk of developing the disease, remains unproved. In this article we review the current literature present on carotenoids and focus particularly on the controversial evidence that retinal carotenoids are protective against age-related macular degeneration.

Methods

Medline and Embase search.

Results

Age related macular degeneration

Definition and grading

In 1995 the International Age Related Maculopathy (ARM) Study Group published the international classification and grading system for age related maculopathy and age related macular degeneration²³. In this article all age related macular changes are referred to as age related maculopathy (ARM). Age related macular degeneration (AMD) is a term reserved for the late stages of ARM²³. Dry AMD refers to geographic atrophy, and exudative is characterised by subretinal haemorrhage, detachment of retinal pigment epithelium (RPE), choroidal neovascularization (CNV), or retinal scarring. Once patients have reached the late stage of this disease, vision loss cannot be restored²⁴ and low vision aids are the only known help.

AMD remains the leading cause of legal blindness in the elderly population in the Western world,^{25,26,27}. The risk for AMD has been strongly linked to greater age²⁸, positive family history of AMD²⁹, smoking^{30,31}, female gender³², and finally the high intake of saturated fat has been demonstrated to be related to early ARM as shown in the Beaver Dam Eye Study³³. Reports vary on the relationship between light iris colour and the severity of AMD or increase risk of for ARM^{34,35,36,37}. It is estimated that 1.6% of the population in the 50-to 65-year-old age group is affected, rising to 30% in the over-75 year-old age group³⁸.

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Dietary sources and ocular antioxidant vitamin and mineral supplements

Of the two carotenoids, lutein plays the predominant role. In fact, the raw product from which lutein and zeaxanthin are derived contains a complex of both, the vast majority being lutein.

There is no cost-effective process to separate the two, nor is there clinical imperative to do so.

Therefore, when products are said to contain lutein, they also contain small amounts of zeaxanthin.

Both of these compounds are fat-soluble and, similar to other fat soluble compounds, they are best tolerated when taken with meals. Since vitamin A and lutein compete somewhat for absorption, the content of vitamin A is reduced or eliminated in many nutraceutical products.

Both vitamin A and lutein provide good antioxidant protection as well as free radical scavenging. However, lutein actually accumulates in the macular pigmented tissues whereas vitamin A does not.

Lutein is a common carotenoid found in most fruits and vegetables, while zeaxanthin is present only in minute quantities in most fruits and vegetables^{39,40}. Dietary sources of zeaxanthin are limited to greens, certain yellow/ orange fruits and vegetables such as corn, nectarines, oranges, papaya and squash. Orange pepper is recently found to have a high amount of zeaxanthin⁴⁰ and the dried fruit of *Lycium barbarum* (*fructus lycii*) prescribed by the Chinese herbalist as a therapeutic agent for a number of eye diseases, has been shown to have a high content of zeaxanthin but negligible amount of lutein⁴¹.

The highest mole percentage of both lutein and zeaxanthin can be found in egg yolk and maize⁴⁰. Substantial amounts of lutein are also known to be found in melon, spinach⁴¹, collards, kale⁴², and guava. In 1998, the United States department of Agriculture (USDA) updated their Carotenoid database for foods to include the concentrations of lutein and zeaxanthin in the most common fruits and vegetables consumed.

(<http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html>).

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The pharmaceutical industry also provides patients with various brands of ocular vitamin supplement products all claiming superiority over their competitors. Some of the brands of these ocular vitamins include: I Caps, Maxivision, Ocuguard, Ocuville, Ocuville Extra, Ocuville PreserVision, Ocuville Lutein, and Vizion. Supplementation with foods rich in lutein and zeaxanthin¹⁹ or with lutein rich supplements^{21,22} increases macular pigment density in most, but not all, human subjects. Nutritional supplements are therefore promoted actively by the vitamin industry in the United States to individuals at risk for AMD. Yet the benefits of ocular antioxidant carotenoid containing vitamin and mineral supplements in patients with ARM, or those at risk of developing the disease remain unproved. The relation of fasting plasma levels of retinol, ascorbate, alpha-tocopherol, beta-carotene and the use of vitamin supplements has shown that alpha tocopherol, and an antioxidant index including alpha tocopherol, beta-carotene, and ascorbate were protective for ARM⁴³. However, no evidence of the protective effect of vitamin supplements was found in this study. In other studies discordant responses of serum and retina to dietary supplementation were observed. Serum lutein increased rapidly after supplementation in individuals, but macular pigment density increased only after several weeks of supplementation^{19,21,44}. Some studies have shown no effect of supplementation with purified or synthetic beta-carotene on the concentrations of several plasma carotenoids^{45,46,47,48}. In contrast, other studies have shown that purified or synthetic beta-carotene can diminish concentrations of lutein^{49,50,51}. Hammond et al have reported that out of 13 subjects given supplemental dietary sources of lutein and zeaxanthin 2 subjects were retinal non-responders- that is, they had significant increases in serum lutein, but not in macular pigment density¹⁹. Recently the evidence of a higher incidence of cancer among cigarette smokers who received beta-carotene supplements in 2 studies^{52,53} was reported. Although beta carotene is considered safe because its conversion to vitamin A is limited⁵⁴ the ATBC study reported a significantly higher mortality among treated than non-treated subjects. To our knowledge published data concerning the toxicity of lutein and zeaxanthin or the optimum dosage or combination of these antioxidant vitamin/ mineral supplements is lacking. The Age-Related Eye Disease Study

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(AREDS), under the auspices of the National Eye Institute of the National Institutes of Health, is carefully following two large cohorts of patients with AMD – one group is being treated with an OcuVite formula, the other with a placebo. When the results of this study begin to be released in five to ten years, further guidance may become known.

There seems to be some support in early clinical and epidemiological studies for the association of zinc and antioxidant nutrients with ARM. In a small clinical trial, high-dose zinc supplementation has been reported to reduce the loss of visual acuity in patients with macular degeneration⁵⁵. Yet other studies were only weakly supportive of the protective effect of zinc on the development of early ARM⁵⁶. More recently, the Age-Related Eye Disease Study (AREDS), research group found a beneficial effect for supplementation with a combination zinc, vitamin E, vitamin C, and beta-carotene in individuals at high risk for disease progression to advanced AMD⁵⁷. Results of this study showed that for patients at high risk of developing advanced stages of AMD, use of the combination of antioxidants and zinc supplements reduced that risk by 25%. For the same group, the risk of vision itself was reduced by 19%. Prospective studies conducted over time, with greater variability in zinc intake in the Beaver Dam population are under way and shall provide further estimates on the protective effect of zinc.

Transport and uptake mechanisms of the carotenoids

The biochemical mechanisms that mediate the selective uptake, concentration, and stabilisation of the of the macular carotenoids are unknown. In lower animals, such as lobsters and cyanobacteria, specialised carotenoid-binding proteins perform these tasks. Much less is known about carotenoid-binding proteins derived from vertebrates, yet it has been hypothesised that comparable carotenoid-binding proteins may have a similar role in the human macula. In the human blood stream, high-density lipoprotein (HDL) is the major carrier of lutein and zeaxanthin, while carotenes are preferentially carried by low-density lipoprotein (LDL)⁵⁸. In the mammalian eye, it has been reported that retinal tubulin binds macular carotenoids⁵⁹, possibly as a site for passive deposition in the tissue. Further postulations included the

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assumption that human macular membranes could be a rich source of specific binding proteins for the macular carotenoids, especially since many plant and invertebrate carotenoid-binding proteins are known to be membrane associated^{60,61}. In a recent report, xanthophyll-binding proteins (XBP) were partially purified and isolated from the human macula and retina and it was shown that lutein and zeaxanthin bind specifically to these proteins⁶². Available evidence further suggests the presence of tissue competition for plasma carotenoids. The concept that adipose tissue and retina may compete for dietary lutein has been suggested⁴⁴, and the interactions between carotenoids during intestinal absorption has also been investigated⁶³. It has hypothesised that if adipose tissue and liver compete with the retina for dietary lutein as suggested by observations in human subjects⁴⁴, macular pigment may be more effectively increased through supplementation with zeaxanthin than with lutein (preferentially absorbed by fat). There is no evidence in literature suggesting that zeaxanthin can be converted to lutein in serum or retina, but the reverse has been proposed by some authors^{64,65}. Dietary lutein may serve as a precursor for the very high concentrations of zeaxanthin found in the primate fovea⁶⁴, and conversion of lutein to mesozeaxanthin has been suggested⁶⁶.

Controversial evidence on the beneficial effects of carotenoids and other antioxidant vitamins in modulating the course of AMD

Epidemiological evidence

Some epidemiological evidence suggest a beneficial role for carotenoids and antioxidant vitamins in the prevention of AMD^{31,67,68}. In contrast, in a case control study consisting of subjects with late AMD, exudative AMD, and retinal pigment abnormalities with the presence of drusen, and an equal number of control subjects, the serum concentrations of lutein and zeaxanthin were found to be unrelated to the risk of incidence of AMD⁶⁹. Lower risk for macular degeneration has been associated with the consumption of food sources of these

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carotenoids⁷⁰, with overall level of lutein and zeaxanthin in the diet^{68,71} or with higher levels of these carotenoids in the blood³¹ or retina^{72,73}. However, in several studies, these associations were not observed^{56,70,74,75} or were observed only in population subgroups⁷¹. Other epidemiological studies have reported a protective effect against lung cancer of foods rich in beta-carotene⁷⁶. This finding has been contradicted in two recent studies in which supranutritional doses of beta-carotene (25-50mg/day) supplemented to smokers during 6y had a higher incidence of lung cancer than did the placebo-treated control subjects^{52,77}.

Experimental evidence

The body of evidence available from studies in laboratory animals that supports associations between the intake of antioxidant nutrients and ARM is inconsistent. Several antioxidant nutrients known to affect retinal degeneration in animals have not been found to consistently correlate with macular degeneration in humans. In macaque monkeys fed diets devoid of all sources of carotenoid pigment, levels of these pigments in the macula disappear and retinal abnormalities (drusen formation), an early sign of ARM appear⁷⁸. In contrast, inverse associations with several carotenoids in the serum^{43,69,75} or diet and early ARM have not been documented in studies in humans.

In a recent study done on rhesus monkeys serum levels and macular density of zeaxanthin was raised by feeding monkeys a carotenoid-containing fraction of fructus lycii also known as Gou Qi Zi⁷⁹. This was contrary to the study by Snodderly et al⁸⁰ where no change in the concentration of serum lutein was noted after supplementation of zeaxanthin in squirrel monkeys.

A potential animal model in which to study the protective effects of these carotenoids is the quail. The quail retina has been shown to selectively accumulate lutein and zeaxanthin^{81,82} and quail retina has been shown to exhibit age-related loss of photoreceptors⁸³. Preliminary studies indicate an inverse correlation between the level of zeaxanthin in quail retina and light-induced cell death^{84,85}. Further studies report that quail fed for 6 months on zeaxanthin-supplemented

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diets have an almost 5-fold elevation in retinal zeaxanthin, and a more than 45-fold increase in zeaxanthin concentrations in serum, liver and fat ⁸².

Reports on other antioxidant vitamins are also controversial. Supplementation of rats with vitamin C has been reported to reduce retinal damage due to intense light exposure ⁸⁶. However, several other human studies that have examined levels of vitamin C in the serum ^{43,67} or foods ^{68,70} have found similar statistically significant associations. Reports have shown that animals with diets deficient in vitamin E have increased retinal damage ⁸⁷, although supplementation with this nutrient does not protect against light damage ⁸⁸. In human studies, one study ⁴³, but not 3 others ^{67,69,75} have found low levels of this nutrient in the serum to be associated with lower risk for various forms of ARM.

Clinical evidence:

Of the hypothesis that macular pigment protects against ARM were the topographic studies of atrophic AMD showing that the region most vulnerable to damage lies within the region where the density of the macular pigment is low ^{89,90}. In donor eyes with bull's eye macular degeneration it was found that the area of preserved central retina corresponded to the area containing the macular pigment ⁹¹. Recently an autopsy study has reported that eyes from donors with a history of AMD had lower levels of macular carotenoids than eyes without a known history of AMD ⁷², although studies relying on post mortem analysis and retrospective reviews of clinical records after death have substantial limitations.

In some studies MP density was changed by dietary modification ¹⁹ or through lutein supplementation ^{21,22}. In others, some subjects failed to show a change in MP density after increasing their dietary intake of lutein and zeaxanthin ¹⁹. Results in case-control studies have indicated that the risk for exudative AMD is reduced in subjects with elevated levels of lutein and zeaxanthin in the serum ⁶⁷ or diet ⁶⁸ but this correlation was not observed in some population-based studies ⁶⁹.

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Reports have also been made on the influence of factors such as sex, and smoking on the relation between MP density and serum concentrations of lutein and zeaxanthin ^{92,93}, yet these associations were evaluated in small study samples.

Effect of light and genetic influence on ARM

It has been suggested that the exposure of the retina to light can promote the development of macular degeneration ⁹⁴. Increased risk for late AMD was associated with increased exposure to blue and visible light in a case control study of Chesapeake watermen ^{95,96} and with increased exposure to sunlight in the Beaver Dam Eye Study ⁹⁷. Light exposure can also increase the production of free radicals in the lens and retina ⁹⁸. Epidemiological data to support a damaging role of light in macular degeneration is inconsistent ⁹⁹, although the difficulty in capturing actual light exposure over many years in the participants studied must be taken into account. Several results on genetic studies with ARM have been published. First-degree relatives of ARM patients are between 2 to 4 times greater at risk of developing ARM in comparison to controls ¹⁰⁰. Twin studies have shown high levels of concordance of the disease among monozygous sibs ^{101,102}. Careful segregation analyses on a large study of 564 families suggest that a single major gene accounts for 89-97% of the genetic variability or 55-57% of the total variability ¹⁰³. Even so, relatively little is known about identified genetic risk factors for ARM and controversial reports exist supporting genetic variations ^{104,105}.

Discussion

The information available provides an indication that the carotenoids, lutein and zeaxanthin, may play a role in modulating the course of AMD, yet critical evidence of the beneficial effect has not been found, and crucial information for the most effective design of clinical trials is needed ¹⁰⁶. For the clinician it is clear that this area of research is only beginning to evolve and

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further research is indicated. There is no doubt that any scientific support for the use of these carotenoids and /or other vitamins or minerals with antioxidant properties will boost the supply of these supplements on pharmacy shelves, despite the unproved benefits. As of yet the long-term physiological consequences of taking ocular vitamin supplements are unknown, and until the optimum combination and dosage of these ocular antioxidant vitamins and minerals has been proven and their long-term safety established, the routine prescription of vitamin/mineral supplements cannot be justified.

We finally suggest that clinicians inform their patients that there is no agreement among scientists and doctors to the benefit of supplementation and we urge them to be cautious when prescribing ocular vitamin/mineral supplements. However, patients with ARM or at risk of developing the disease, should be encouraged to eat a balanced diet rich in fruits and vegetables, and in particular they should be informed by they clinician on the dietary sources rich in these carotenoids. We further recommend patients to wear UV protective lenses and a hat or cap when outdoors and suggest they see their primary care physician to treat any hypertension, hypercholesterolemia or potentially compromising vascular disease. We truly hope that future investigations on the role of nutrition, light exposure and genetics help reduce the incidence of this debilitating disease.

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