

Review

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## 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:** Recent evidence introduces the possibility that lutein and zeaxanthin, carotenoids found in a variety of fruits and vegetables may protect against the common eye disease of macular degeneration. This potential and the lack to slow the progression of macular degeneration, has fueled high public interest in the health benefits of these carotenoids and prompted their inclusion in various supplements. The body of evidence supporting a role in this disease ranges from basic studies in experimental animals to various other clinical and epidemiological studies. Whilst some epidemiological studies suggest a beneficial role for carotenoids in the prevention of AMD, others are found to be unrelated to it. Results of some clinical studies indicate that the risk for AMD is reduced when levels of the carotenoids are elevated in the serum or diet, but this correlation is not observed in other studies. Published data concerning the toxicity of the carotenoids or the optimum dosage of these supplements is lacking.

**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 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. Future investigations on the role of nutrition, light exposure, genetics, and combinations of photodynamic therapy with intravitreal steroid (triamcinolone-acetonide) injections hold potential for future treatment possibilities.

### Introduction

The two major carotenoids in the human macula and ret-

ina are lutein and zeaxanthin [1,2]. Similar to  $\beta$ -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 [6-8], 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 irreversible vision loss in the elderly population in the USA and the Western world. 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 group. As the proportion of the elderly in our population increases, the public health impact of AMD will become even more severe. 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 [12,16-18]. Supplementation with foods [19-21] 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 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 degeneration [23]. In this article all age related macular changes are referred to as age related maculopathy (ARM). ARM is a degenerative disorder involving the retinal pigment epithelium, choriocapillaries and retina which primarily, but not exclusively, affects the macular region. Symptoms of ARM include metamorphosia, impaired light adaptation and decreased central vision. Age related macular degeneration (AMD) is a term reserved for the late stages of ARM [23]. AMD has been categorised in two forms, an exudative form characterised by subretinal haemorrhage, detachment of retinal pigment epithelium (RPE), choroidal neovascularization (CNV), or retinal scarring and a "dry" form which includes geographic atrophy. Once patients have reached the late stage of this disease, vision loss cannot be restored [24] 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 [25-27]. The risk for AMD has been strongly linked to greater age [28], positive family history of AMD [29], smoking [30,31], female gender [32], and finally the high intake of saturated fat has been demonstrated to be related to early ARM as shown in the Beaver Dam Eye Study [33]. Reports vary on the relationship between light iris colour and the severity of AMD or increase risk of for ARM [34-37]. 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 group [38].

#### Dietary sources of lutein and zeaxanthin

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 zeaxanthin [40] 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 lutein [41].

The highest mole percentage of both lutein and zeaxanthin can be found in egg yolk and maize [40]. Substantial amounts of lutein are also known to be found in melon, spinach [41], collards, kale [42], 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 vegetable consumed. <http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html>.

#### *Pharmaceutical ocular vitamin and mineral supplements – the vitamin/mineral supplement controversy*

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, OcuVite, OcuVite Extra, OcuVite PreserVision, OcuVite Lutein, and Vizion. Supplementation with foods rich in lutein and zeaxanthin [19] 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 ARM [43]. 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 [19,22,44]. Some studies have shown no effect of supplementation with purified or synthetic beta-carotene on the concentrations of several plasma carotenoids [45-48]. In contrast, other studies have shown that purified or synthetic beta-carotene can diminish concentrations of lutein [49-51]. 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 density [19]. 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 limited [54], 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 (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.

#### *The impact of zinc and other antioxidants on ARM*

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 degeneration [55]. Yet other studies were only weakly supportive of the protective effect of zinc on the development of early ARM [56]. 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 AMD [57]. 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 carotenoids [59], possibly as a site for passive deposition in the tissue. Further postulations included the 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 proteins [62]. 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 suggested [44], and the interactions between carotenoids during intestinal absorption has also been investigated [63]. It has hypothesised that if adipose tissue and liver compete with the retina for dietary lutein as suggested by observations in human subjects [44], 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 fovea, [64] and conversion of lutein to meso-zeaxanthin has been suggested [66].

### **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 AMD [69]. Lower risk for macular degeneration has been associated with the consumption of food sources of these carotenoids [70], with overall level of lutein and zeaxanthin in the diet [68,71], or with higher levels of these carotenoids in the blood [31]. However, in several studies, these associations were not observed [56,72] or were observed only in population subgroups [71]. Other epidemiological studies have reported a protective effect against lung cancer of foods rich in beta-carotene [73]. This finding has been contradicted in two recent studies in which supra-nutritional doses of beta-carotene (25–50 mg/day) supplemented to smokers during 6 y had a higher incidence of lung cancer than did the placebo-treated control subjects [52,74]. *Please see table 1, additional file 1.*

#### *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 appear [75]. In contrast, inverse associations with several carotenoids in the serum [43,69] 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 Zi [76]. This was contrary to the study by Snodderly et al [77] 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 [78,79] and quail retina has been shown to exhibit age-related loss of photoreceptors [80]. Preliminary studies indicate an inverse correlation between the level of zeaxanthin in quail retina and light-induced cell death [81,82]. Further studies report that quail fed for 6 months on zeaxanthin-supplemented 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 [79].

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 [83]. 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 [84], although supplementation with this nutrient does not protect against light damage [85]. In human studies, one study [43], but not 3 others [67,69,86], 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 AMD was a study in which risk factors for AMD namely, age and advanced disease in the fellow eye, were shown to be associated with a relative absence of macular pigment [87]. 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 [88], 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 or through lutein supplementation [21,22]. In another study, some subjects failed to show a change in MP density after increasing their dietary intake of lutein and zeaxanthin [19]. Evidence in favour of changing the dietary intake of fat soluble vitamins to protect against AMD has been contradicted by some authors [89]. 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 [90,91], yet these associations were evaluated in small study samples. *Please see table 2, additional file 2.*

#### *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 [92]. Increased risk for late AMD was associated with increased exposure to blue and visible light in a case control study of Chesapeake watermen [93,94] and with increased exposure to sunlight in the Beaver Dam Eye Study [95]. Light exposure can also increase the production of free radicals in the lens and retina [96]. Epidemiological data to support a damaging role of light in macular degeneration is inconsistent [97], 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 [98]. Twin studies have shown high levels of concordance of the disease among monozygous sibs [99,100]. 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 [101]. Even so, relatively little is known about identified genetic risk factors for ARM and controversial reports exist supporting genetic variations [102,103].

#### *Treatment options for ARM and future hopes*

Some of the clinical approaches to treating AMD include novel laser therapies (photodynamic laser therapy, PDT), surgery (submacular and macular translocation surgery), chemotherapeutic agents (angiogenesis inhibitors such as thalimide, interferon, vascular endothelial growth factor inhibitors), radiation (external beam/ teletherapy or episcleral plaque/brachytherapy), transplantation of retinal pigment epithelium and photoreceptors, and gene therapy.

One of the more promising therapies is photodynamic therapy (PDT). A light activated drug is administered intravenously, followed by a waiting period of several minutes to allow the neovascular network of vessels to bind and absorb the drug. Laser light is then applied to the now pharmacologically-sensitized target tissues resulting in precise demise of the microvascular network. This process spares the overlying elements, whereas surgery and radiation could cause retinal scar formation.

Recently, a combination of PDT along with intravitreal steroid (triamcinolone-acetonide) injections has been

introduced. Steroid compounds are well known antiangiogenic agents which have been suggested as treatment for the choroidal neovascular membranes that cause visual loss in ARM [104,105]. We hope to release the results of the study done on a cohort of patients treated with triamcinolone and PDT, along with a control group of patients treated with PDT, within one year. Much of our hope for successful future treatments also lies in the areas of suppression or modification of neovascular response with novel anti-angiogenic factors and gene therapy.

#### **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 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 their 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.

#### **Additional material**

##### **Additional File 1**

*Summary of major epidemiological studies suggesting or contradicting a beneficial role of the carotenoids or other antioxidants in altering the pathogenesis of macular degeneration.*

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### Additional File 2

Summary of major clinical studies suggesting or contradicting a beneficial role of the carotenoids or other antioxidants in altering the pathogenesis of macular degeneration.

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