Micronutrients in Age-Related Macular Degeneration

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Key Words

Macular degeneration • Nutrition • Micronutrients • Vitamin C • β -Carotene • Vitamin E • Zinc • Lutein • Zeaxanthin • Omega-3

Abstract

Several lines of evidence from in vitro and in vivo studies suggest that specific micronutrients may have beneficial effects in age-related macular degeneration (AMD). Such effects appear to be complex and may include filtering short wavelength light and attenuating oxidative and inflammatory damage as well as other structural and physiological factors. There is clinical evidence for potential benefits from vitamin C, β -carotene, vitamin E and zinc, as well as emerging epidemiological and clinical data for the carotenoids lutein and zeaxanthin and for omega-3 fatty acids. A survey of the literature suggests that some specific micronutrients may be of value in treating or preventing AMD, but further prospective studies are needed to further identify and characterize their effects and place in therapy.

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Introduction

Evidence for the benefit of micronutrients in age-related macular degeneration (AMD) comes from a variety of sources; biochemical, laboratory and animal studies indicate that specific micronutrients may have beneficial effects in filtering short wavelength light, decreasing oxidative and inflammatory damage and lowering apoptosis and angiogenesis, as well as other structural and physiological roles.

However, clinical and epidemiological studies are more direct indicators of potential benefit to patients, and human studies have involved both interventional and observational studies to provide evidence for dietary nutrients and supplements. Some support beneficial effects of good diet alone, whilst others show the effect of supplementary nutrients, at doses higher than can usually be obtained from diet alone. There is consensus about a potential beneficial effect of lutein/zeaxanthin and long-chain omega-3. On the other hand, there are still some inconsistencies in reported benefits for different micronutrients and micronutrient combinations.

Such conflicting reports from clinical studies reflect the multifactorial nature of macular degeneration, wide variety of population nutrient intakes, different nutri-

Table 1. AREDS categories 3 and 4 criteria

Category 3: one or two eyes with
– 20 intermediate size drusen (if soft drusen)
– or 65 intermediate size drusen (if no soft drusen)
– or one large druse >125 μm
– or noncentral geographical atrophy
Category 4: one eye only with
– advanced AMD (central geographical atrophy/choroidal neovascularization)
Other information
– intermediate drusen = 63–125 μm
– 125 μm = vein size at disc margin
– vision must be 6/9 or better in best eye

There is a high level of evidence for reduced risk of development of advanced AMD using high-dose supplements in such patients.

ent doses and combinations in different trials, varying plasma levels and bioavailability depending on the individual and the variety of different genetic backgrounds.

The objective of the present review is to summarize the clinical and epidemiological evidence for the benefits of each of the major groups of micronutrients.

Vitamin C, β -Carotene, Vitamin E and Zinc

The strongest evidence for the benefit of these micronutrients comes from the extensive Age-Related Eye Disease Study (AREDS) [1], which was a large randomized controlled trial of ocular supplements in patients with a range of AMD. In patients classified with stage 3–4 AMD (table 1), it demonstrated a 25% reduction in the rate of deterioration to the late manifestations of the illness over a 5-year period. The supplements (vitamin C, β -carotene, vitamin E and zinc) were given in doses greater than could be achieved through diet alone for a long period of time without significant side effects. Of note is that a significant proportion of the population was already on supplements and also that the complete combination of micronutrients was required; subgroups with only some of the nutrients failed to show significant benefit. It is also notable that the beneficial effect was proven only for conversion from early AMD to neovascular AMD, but not for that from early AMD to atrophic AMD. Furthermore, the genetic background seems to influence the impact of zinc supplementation.

Some results from epidemiological studies on these nutrients have been contradictory; for example, the Pathologies Oculaires Liees à l'Age (POLA) Study (1999) [2] showed that the risk for late AMD is reduced by 82% in people with a high plasma level of vitamin E compared to people with a low level. The Rotterdam study (2005) also showed a decreased risk for AMD in subjects with high dietary intakes of β -carotene, vitamins E and C and zinc [3]. However, Taylor et al. [4] showed no association of vitamin E with AMD, and the Physicians' Health Study [5] failed to show any marked benefits for vitamins C or E. This perhaps reflects a greater dependence of this group of compounds on other confounding factors such as absorption rates, interaction with other micronutrients, exact doses of any oral supplements, bioavailability and baseline dietary intakes.

Overall, evidence for potential benefit of this group of micronutrients predominates. In addition to the large-scale AREDS study of nutritional supplements, protective associations with high serum levels [6, 7] and higher dietary intakes have been described [3, 8, 9].

It should be noted that high β -carotene intakes are contraindicated for smokers due to a potential increased risk for lung cancer. Continued need for β -carotene is being investigated in a follow-up of the AREDS study (AREDS II) along with the newer micronutrients discussed below. Pending the results of this study, many formulations have replaced β -carotene with other antioxidants.

Overall, for this group of micronutrients, there is the strongest level of evidence for benefit of oral supplements based on a large prospective multicenter randomized controlled trial. The benefits of these dietary and supplemental micronutrients have been robustly demonstrated to have a significant clinical effect. However, these benefits may be limited to precise populations and combinations of the nutrients.

Lutein and Zeaxanthin (Carotenoids)

This group of micronutrients has been investigated more recently. They are not usually associated with recommended daily amounts and have been available in the form of oral supplements more recently than vitamins A, C and E and zinc.

Most large-scale epidemiologic observational studies agree with the findings of beneficial effects of dietary intake of carotenoids, such as the Eye Disease Case-Control Study (USA) [10]. Studies based on plasma levels also found a correlation between high levels of lutein/zeaxan-

thin in the plasma and low risk of AMD, e.g. the POLA Study [11] and Gale et al. [12].

Randomized controlled trials are scarce at present. A small randomized study using lutein supplementation in early AMD (Lutein Antioxidant Supplementation Trial) [13] showed a beneficial effect of lutein on the increase in macular pigment density. The evidence is not entirely in support of a protective role for these carotenoids; for example, the Carotenoids in Age-Related Eye Disease Study demonstrated a difference with higher levels of carotenoids only when analysis was limited to women under 75 years [14].

These nutrients are sequestered in the macula in a measurable form as macular pigment. Various studies have demonstrated an increase in macular pigment with carotenoid intake [15, 16].

Overall, various laboratory and clinical studies indicate that an increased intake of carotenoids may be associated with a reduced risk for AMD.

Omega-3

Omega-3 long-chain polyunsaturated fatty acids have been the most recent of those mentioned to have emerged as having potential benefit to those with AMD or those at risk of AMD. Although there have been no large-scale randomized trials published yet, observational data show a strong effect, perhaps greater than that of the other micronutrients discussed so far, comparing many thousands of patients overall. There is also a greater degree of consistency amongst different studies in showing significant benefits. For example, Seddon et al. [17] showed a relationship between omega-3 intake and reduced AMD. The AREDS report number 23 [18] and SanGiovanni et al. [19] showed that exudative AMD risk decreases with dietary omega-3 intake. Indeed, a meta-analysis of 9 studies and 88,974 participants demonstrated that high dietary intake of omega-3 fatty acids was associated with a 38% decreased risk for late AMD. Moreover, fish consumption at least twice a week was associated with a reduction in both early (24% reduction) and late (33% reduction) AMD [20].

Other population studies confirm this link between dietary intake of omega-3 and lower levels of AMD [21–23]. The US Twin Study of Age-Related Macular Degeneration [17], the Nurses' Health Study and the Health Professionals Follow-Up Study [24] concur, as do studies by Christen et al. [25], Seddon et al. [17], Swenor et al. [26] and Merle et al. [27], as well as the POLA and Nutrition

Table 2. An overview of micronutrient dosages

	Dosages in prospective studies, mg/day		European limits mg/day	Dosage variations mg/day
Vitamin C	500	AREDS 1	180	300–500
Vitamin E	266	AREDS 1	30	100–266
Zinc	80/25	AREDS 1/2	15	25–80
Copper	2	AREDS 1		
Lutein	10	AREDS 2		6–20
Zeaxanthin	2	AREDS 2		0–2
Omega-3	1,000	AREDS 2		600–4,000

(POLANUT) study [28]. There is thus a broad consensus on the association between high omega-3 intake and low levels of AMD of all stages.

Sufficient omega-3 long-chain polyunsaturated fatty acids are mainly derived from fish and seafood and are difficult to obtain from purely vegetarian sources.

Studies in the field of omega-3 have been ongoing for the last decade. Although there have not yet been any large randomized controlled trials published, there is strong consistency of results from the studies on omega-3, and the level of benefits that are theoretically gained appear to be the highest from amongst all micronutrient groups.

Conclusions

Various findings are in favor of a role of several specific micronutrients in the treatment or prevention of AMD. Patients with AREDS level 3–4 AMD (table 1) should be prescribed supplements as per AREDS, which appears to have an effect beyond that which could be obtained through diet alone. For patients with earlier forms of AMD, clear evidence is still lacking.

Dietary intakes of vitamin E, zinc and carotenoids are low in Europe, and some vulnerable groups lack sufficient vitamin C intake. Omega-3 intake is also poor in the aged population in Europe [29, 30], but an increase in the omega-3/omega-6 ratio can be obtained by regular oily fish consumption. Thus, it is important to encourage a healthy balance of all micronutrient subgroups as part of a balanced healthy diet, along with good fluid intake. Recommended dosages for these micronutrients, according to present evidence, are summarized in table 2.

Vitamin A, lutein and zeaxanthin are obtained from peas, spinach, kale, watercress, turnip, sprouts, lettuce, broccoli and yellow foods (corn, orange, eggs). Vitamin C

is sourced from citrus fruits and juices, kiwi, cabbage and cauliflower. Vitamin E can be provided by wholegrain cereals, vegetable oils, nuts, turnips, beetroot, tomatoes, pumpkins, asparagus and broccoli.

Zinc is present in beef, pork, chicken, oysters, fortified cereals, baked beans, yoghurt and chickpeas, whilst omega-3 fatty acids are principally obtained from oily fish and seafood and specific vegetable oils (rapeseed, soybean, walnut).

Many patients may find it difficult to maintain adequately high intake of key micronutrients, due, for example, to disliking or being prohibited from eating key foods, difficulty eating in general, difficulty accessing key foods or general difficulties in maintaining a diet rich in all the above micronutrients at all times.

For these patients, supplements may be preferred, and those containing all three groups of micronutrients described may be prudent.

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