Macular pigments: lutein and zeaxanthin

Over 600 carotenoids have been identified to the present date; however, only about 50 are found in normal human diets.

Vegetables are the only source of carotenoids. Macular pigments (MP) consist of two natural xanthophylls from the carotenoid family: lutein (L) and zeaxanthin (Z), as well as the products of their transformation in the body, notably meso-zeaxanthin[(16)].

These pigments are not synthesised by the human body and have been investigated for their ability to promote visual health.

Macular pigments are found in photoreceptor axons in the pigment epithelium and in the external segment.

The latter contains very high levels of polyunsaturated fatty acids, at a high risk of oxidation[(17,18,19)]. Macular concentrations of L and Z decrease with age, which exacerbates the harmful effects of blue light on photoreceptors.

Their protective mechanism is unknown; however, two mechanisms have been proposed: macular pigments may act as an optical filter, due to their ability to absorb blue light, and they are strong antioxidants, neutralising free radicals generated by light [(20,21)].

Several observational studies have demonstrated a correlation between plasma L and Z levels, macular pigment density and a lower risk of AMD.

Increased intake of L and Z supplements resulted in increased plasma levels, which were positively and significantly associated with the optical density of macular pigment[(22)].

Furthermore, various well-conducted population-based longitudinal studies have suggested that high dietary antioxidant levels, specifically L and Z, may have protective and beneficial effects, delaying progression to advanced AMD.

The following are some examples of observational studies investigating the relationship between dietary and/or serum antioxidant levels and the risk of AMD.

EDCCS (Eye Disease Case-Control Study): this study, published in 1992, demonstrated a high significant inverse relationship ($p= 0.001$) between the prevalence of AMD and serum L and Z concentrations: the risk of neovascular lesions was 70% lower in subjects with the highest serum L and Z concentrations, compared to those with the lowest levels (odds ratio: 0.4; 95% CI: 0.2-0.6; $p= 0.0001$)[(23)].

In 1994, the same group concluded that the risk of developing the most severe form of macular degeneration was 43% lower in individuals who consume large amounts of fruits and vegetables rich in L and Z (6mg/day) (odds ratio: 0.57; 95% CI: 0.35-0.92; p= 0.02) (24).

Another observational study conducted in 2002 showed that average L and Z levels were 32% lower in AMD eyes than in control eyes, in elderly subjects, provided the latter were not consuming high doses of L supplements.

This study demonstrated that average levels of macular pigments in patients who had begun to regularly consume supplements containing high doses of L (> 4 mg/day) after the initial diagnosis of AMD were within the normal range and significantly higher than in AMD patients not consuming this supplementation(25).

In 2006, the POLA study (Pathologies Oculaires Liées a l'Age) found that high plasma L and total L and Z concentrations are associated with a reduced risk of age-related maculopathy (ARM)(26).

CAREDS (Carotenoids in Age-related Eye Disease Study): in this observational study, conducted in 2006, no statistically significant differences in intermediate AMD prevalence were found between subjects with high and low dietary intakes of L plus Z.

However, analysis of a sub-group of women under 75 with stable L plus Z intakes revealed a reduced risk of this subtype of AMD in association with a high dietary intake of those antioxidants.

A diet rich in L plus Z may protect against intermediate AMD(27).

In 2007, AREDS (Age-related Eye Disease Study report 22), a case-control study with 4519 participants, concluded that a high dietary intake of L and Z was independently associated with a decreased likelihood of neovascular AMD, geographic atrophy, and large and extensive drusen(28).

Up to the present date, seven important interventional studies have investigated the role of L supplementation in AMD patients(29-35).

Of the aforementioned studies, two assume major importance: LAST (Lutein Antioxidant Supplementation Trial) was the first study to show that L supplementation improved visual function in AMD patients.

Furthermore, it reinforced the notion that AMD is a nutrition-responsive disease.

The results of this trial were confirmed in 2004.

In this trial, 90 AMD patients received either a daily supplement consisting of 10mg of L, a supplement consisting of 10 mg of L and a mixed antioxidant formula (containing vitamin A, beta-carotene, vitamin C, vitamin E, vitamin B complex, copper, zinc,

manganese, magnesium, selenium and other minerals), or placebo, for 12 months.

Results showed that patients receiving the L supplement displayed significant improvements in several objective visual function measures (contrast sensitivity or visual acuity) when compared to the placebo group.

Slightly better results were observed in subjects consuming the combined supplement(34). CARMA (Carotenoids in Age-related Maculopathy Study) was an important European intervention study, published in 2008.

This randomised, double-blind clinical trial of antioxidant supplementation versus placebo enrolled 433 patients from two centres in Ireland, with signs of early AMD of sufficient severity in at least one eye, or any level of AMD in one eye and late AMD (neovascular AMD or central geographic atrophy) in the fellow eye.

The aim of the CARMA Study was to investigate whether administration of 12 mg of L and 2 mg of Z, in combination with antioxidants (120 mg of vitamin C, 15mg of vitamin E, 20mg of zinc and 0.4 mg of copper), had a beneficial effect on visual function and/or was able to delay progression of early to late disease stages.

The primary outcome was improved or distance visual acuity was preserved at 12 months.

Although no beneficial effects were demonstrated in the primary outcome measure at the stated end point (12 months), secondary outcomes favoured the supplemented group[(35)].

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