

Protecting against AMD

The role of the macular carotenoids

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Age-related macular degeneration (AMD) is the leading cause of blindness in the western world, estimated to affect approximately 497,000 people in the UK and the Republic of Ireland¹ and more than 1.75 million individuals in the United States; these figures are expected to double by 2020.² This increasing prevalence worldwide is largely attributable to increasing longevity and lifestyle changes associated with western society.

Although the pathogenesis of AMD remains poorly understood, there is now a growing consensus that one or more of the following processes contribute to the condition: inflammation; oxidative stress; cumulative blue light damage; retinal pigment epithelial (RPE) cell dysfunction; and reduced foveolar choroidal circulation. It is now agreed definitively, however, that oxidative stress and cumulative blue light damage are of major importance in AMD development.³⁻⁵ Interestingly, both processes are compatible with every other hypothesized mechanism of AMD pathogenesis.

The importance of three carotenoids

The macula is responsible for detailed central and colour vision. Three dietary carotenoids — lutein, zeaxanthin and meso-zeaxanthin — accumulate within the macula, and are collectively referred to as macular pigment (MP). MP is yellow in colour, and therefore absorbs blue light; it is also a powerful antioxidant, which neutralizes free radicals. Since blue light damage and free radicals are known to contribute to AMD, it is unsurprising that this pigment is believed to protect against this condition. In fact, there is now an increasing body of scientific evidence which supports such a notion. Recent research has shown that individuals who have a relative lack of MP are at increased risk of developing AMD.⁶

In short...

Dr John Nolan and colleagues discuss the growing body of evidence that suggest a protective role of macular pigment in the retina's defence against AMD. Specifically, he notes the importance of the three carotenoids, which make up the pigment — lutein, zeaxanthin and meso-zeaxanthin — and suggests that protection is offered through their ability to protect against chronic damage caused by light and oxygen. He presents as a case study an AMD patient who showed significant improvement upon receiving a course of lutein, zeaxanthin and meso-zeaxanthin supplementation.

This article specifically discusses the rationale and available evidence that supports the use of macular carotenoids in the prevention of AMD.

Oxidative stress explained

The hypothesis that oxygen, an essential requirement for all living organisms, is also a potentially toxic substance is becoming increasingly understood and accepted. Oxidative stress refers to damage caused by unstable and reactive oxygen intermediates (ROIs) and, as mentioned above, there is a growing body of evidence to suggest that damage caused by ROIs plays a role in the pathogenesis of AMD.

ROIs can be classified according to their reactivity towards biological targets, their site of production, their chemical nature, or their free radical or non-radical subgroups. In this article, we describe ROIs in terms of their free radical and non-radical subgroups.

Free radicals are molecules that contain one or more unpaired electrons in their outer orbits.⁷ In order to achieve a stable state, these unstable molecules 'steal' electrons from other molecules (e.g. lipids, proteins, DNA), which are themselves rendered unstable by this reaction, and a cascade of cytotoxic reactions ensues. Non-radicals, such as hydrogen peroxide, contain the full complement of electrons but are, nevertheless, in an unstable state. Antioxidants are molecules that neutralize ROIs: oxidative damage occurs, therefore, when the level of ROIs overwhelms the antioxidant defence system, with consequent cellular damage.⁷

The retina is particularly susceptible to damage by ROIs. There are several reasons for this vulnerability: firstly, there is an extremely high consumption of oxygen within the retina; secondly, the photoreceptors of the retina contain high amounts of polyunsaturated fatty acids (PUFAs). PUFAs are particularly susceptible to free radical damage because their conjugate double bonds are convenient sources of hydrogen atoms, which contain one electron. The retina is also exposed to visible light, which is known to generate ROIs via photosensitization reactions, constantly. Finally, the process of phagocytosis by the RPE is known to generate hydrogen peroxide (non-radical species).⁷⁻¹⁰

Damaging blue light?

Cumulative (short-wavelength) blue light damage represents an environmental factor, which is believed to play a role in the pathogenesis of AMD. Over a lifetime, exposure to visible light (specifically, short-wavelength blue light) causes photo-oxidative damage to the retina,^{4,5} and this damage is mediated

through oxidative stress.⁸ Indeed, the presence of lipid peroxidation products following irradiation of the retina provides strong evidence that cumulative retinal light damage is mediated through ROIs.^{3;11-14} It is generally accepted, therefore, that ROIs, generated by reactions involving short-wavelength irradiation and arterial oxygen, denature PUFAs in the photoreceptors, leading to cell death and AMD.

Does macular pigment provide protection?

Carotenoids are naturally occurring plant pigments. More than 600 of these have been identified to date and this includes those which make up the yellow pigment MP — lutein, zeaxanthin, and meso-zeaxanthin. Meso-zeaxanthin is the only pigment of the three that is found solely within the macula, whereas lutein and zeaxanthin, present in a typical diet, are also found in serum and several other tissues throughout the body. Meso-zeaxanthin is generated at the macula following biochemical conversion from lutein¹⁵ and, although it is not found in a regular diet, it is found in some foods, such as seafood (for example, shrimp and crab), fish (for example, trout and salmon), and turtle.¹⁶

The blue light filtering properties and/or antioxidant activity of MP are believed to confer protection against AMD. MP's peak absorption is at a wavelength of 460 nm (blue light) and, therefore, it functions as an optical filter of blue light. It has been estimated that MP reduces blue light transmission at a pre-receptor level by up to 40%.¹⁷

The antioxidant capability of MP is related to the structure of its carotenoids, which ensures that they themselves do not become radicalized. Kirschfeld et al. were the first to hypothesize that the macular carotenoids act as antioxidants.¹⁸ However, firm evidence of this was provided by Khachik and colleagues, who demonstrated that the presence of direct oxidation products of the macular carotenoids in the human retina.¹⁹

Meso-zeaxanthin offers the most protection

It was Bone and colleagues who originally hypothesized that meso-zeaxanthin was a metabolic product formed in the retina from lutein (i.e. lutein undergoes isomerization of one of its

double bonds and is oxidized to meso-zeaxanthin).²⁰ To test this hypothesis, a team led by Neuringer performed a supplementation study in monkeys.¹⁵ In this study, monkeys that were completely deficient in MP, as a result of lifelong dietary deprivation of the macular carotenoids, exhibited carotenoid accumulation at the macula following supplemental lutein or zeaxanthin for a period of many weeks. Those given pure zeaxanthin were found to have only that carotenoid present in the retina, whereas those fed lutein were found to have both lutein and meso-zeaxanthin, supporting the hypothesis that meso-zeaxanthin is derived from lutein within the retina.

Given that the suggested importance of MP rests on its antioxidant properties and its ability to filter blue light, it is interesting to note that meso-zeaxanthin has been suggested to be more important than lutein and zeaxanthin in relation to these functions. Indeed, studies have shown that meso-zeaxanthin is a more potent antioxidant than zeaxanthin when bound to its retinal binding protein, glutathione S-transferase (GSTP1).²¹ It is also believed that meso-zeaxanthin facilitates a wider range of blue light filtration (because of its orientation within retinal cell membranes). Moreover, meso-zeaxanthin is more closely related to vulnerable photoreceptors at an anatomic level than either lutein or zeaxanthin and is, therefore, ideally located to afford protection against free radical damage to the photoreceptors.²⁰

The case study

A case study recently performed by the Macular Pigment Research Group (MPRG, www.wit.ie/mprg) at the Waterford Institute of Technology, Ireland has shown that a patient with AMD responded significantly to a supplement containing all three of the macular carotenoids (Macushield; Macuvision).

A 64 year old male non-smoker presented with exudative AMD in the left eye (visual acuity 6/18) (**Figure 1**) and macular drusen in the right eye (visual acuity 6/6) (**Figure 2**). His MP level in the right eye at baseline, measured by heterochromatic flicker photometry (HFP) using the Macular Densitometer, was 0.01 optical density units at 0.5 degrees retinal eccentricity (of note, average MP across a number of studies using HFP ranges



Figure 1: Non-mydriatic colour fundus photo showing exudative AMD in the left eye.



Figure 2: Non-mydriatic colour fundus photo showing macular drusen in the right eye.

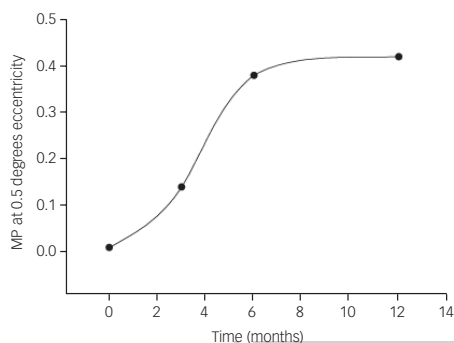


Figure 3: Change in MP level with Macushield supplementation.

between 0.21-0.41 optical density units at 0.5 degrees retinal eccentricity in normal subjects).²²⁻²⁹ Following six months of supplementation with Macushield, this value increased to 0.38, and it was 0.42 following 12 months of supplementation (**Figure 3**). His fundal appearance and visual acuity remained stable over this period of time, although he did report a subjective improvement in visual function. He did not report any other significant lifestyle changes over the supplementation period.

While this individual case study appears positive, future research is essential to further our understanding of the importance of MP, and in particular the role of meso-zeaxanthin, for ocular health and AMD prevention. The MPRG is about to embark on two randomized placebo-controlled clinical trials (one in normal subjects without ocular pathology and one in AMD patients), designed to investigate serum and retinal response to supplemental lutein, zeaxanthin and meso-zeaxanthin, using Macushield. These trials will also examine visual function over the study periods.

In conclusion, there is a biologically plausible rationale, supported by an ever-increasing body of scientific evidence, suggesting that MP protects against AMD. However, it is important to note that the benefits of lutein, zeaxanthin and meso-zeaxanthin, if any, relate to the ability of these compounds to protect against chronic and cumulative damage caused by light and oxygen. We await the outcomes of several important clinical trials which will add to the knowledge regarding the potential benefits of supplemental lutein, zeaxanthin and meso-zeaxanthin in patients with AMD.

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