

The role of macular pigment in the defence against AMD

This article discusses the role of the macular pigment in the defence against the development of age-related macular degeneration (AMD).

Age related macular degeneration (AMD) is the late stage of age-related maculopathy (ARM), and is the leading cause of blind registration in the Western World¹. The disease damages central vision as a result of choroidal neovascularisation with consequential subretinal fibrosis, or by atrophic changes of the retinal pigment epithelium and overlying neurosensory retina. ARM is characterised by the presence of drusen and/or pigmentary changes at the macula, and does not severely affect vision.

The aetiology of ARM and AMD is poorly understood, but there is a consensus that both genetic and environmental factors play a role.

Prevalence of ARM/AMD

AMD is the leading cause of legal blindness in the developed world, and its prevalence is likely to rise as a result of increasing longevity². Estimates suggest that about 30% of people over the age of 75 have ARM and/or AMD, and that there are approximately 60,000 people affected by this condition in Ireland, with 12 million sufferers across Europe. With respect to the visually consequential stage of the disease, it has been estimated that 6-8% of people aged over 75 years suffer from AMD³.

Evans et al have reported that the relative importance of AMD as a cause of blind registration increased dramatically throughout the 20th century⁴. In spite of the high incidence, and severity, of visual impairment associated with AMD, only a small percentage of cases are eligible for treatment⁵. Clearly, the adverse impact of AMD on a patient's quality of life is dramatic, with implications for reading, driving, watching television and recognition of familiar faces⁶.

Pathogenesis of ARM/AMD

Although the pathogenesis of AMD remains uncertain, mechanisms believed to be aetiologically important in the disease process include genetic factors⁷, cumulative light damage^{8,9}, free radical injury¹⁰ and haemodynamic processes¹¹. The outcome appears to be a disturbance of the photoreceptors, and the underlying retinal pigment epithelium, but identification of the primary insult continues to elude us¹².

Retinal pigment epithelium

The retinal pigment epithelium (RPE) participates in several important functions, such as phagocytosis of photoreceptor outer segments and maintenance of the integrity of the blood-retinal barrier¹³. Therefore, RPE dysfunction will inevitably result in disturbances of the overlying neurosensory retina, with consequential deterioration of vision. There is a consensus that the RPE is abnormal in ARM and AMD, and it has been shown that the concentration of lipofuscin, an 'age pigment', in the RPE increases with increasing age¹⁴. Further, it has been shown that lipofuscin compromises RPE cellular function¹⁵.

It is important to note, however, that lipofuscin accumulation in the RPE may result, at least in part, from oxidatively damaged photoreceptor outer segments¹⁷. Also, and of equal interest, lipofuscin generates reactive oxygen intermediates in response to irradiation with blue light, and therefore contributes further to oxidative stress in the local environment¹⁸.

In brief, therefore, it appears that RPE dysfunction contributes to the pathogenesis of ARM/AMD, and that this dysfunction is related to lipofuscin accumulation. To what extent oxidative stress is responsible for the RPE dysfunction remains unknown.

Oxidative stress

Reactive oxygen intermediates (ROI) refer to free radicals, hydrogen peroxide, or singlet oxygen¹⁸. A free radical is a chemical species with an unpaired electron, and the presence of one or more unpaired electrons causes a species to be highly reactive¹⁹. Singlet oxygen and hydrogen peroxide contain their full complement of electrons, but in an unstable reactive state. It is believed that tissue damage by ROI, known as oxidative stress, may contribute to the development of ARM/AMD²⁰.

The retina is an ideal location for the production of reactive oxygen intermediates because of its high oxygen consumption, its exposure to large quantities of solar radiation²¹, its wealth of chromophores and the continual process of phagocytosis by the RPE¹⁸. Further, the retina is particularly vulnerable to damage by ROI because of its high concentration

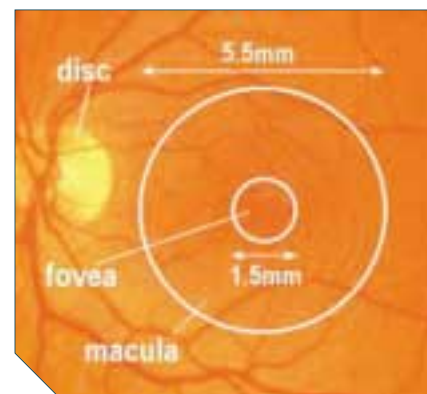


Figure 1
Retina fundus image, showing macula and fovea

of polyunsaturated fatty acids in the photoreceptor outer segments, which are readily oxidised and which can initiate a cytotoxic chain reaction²².

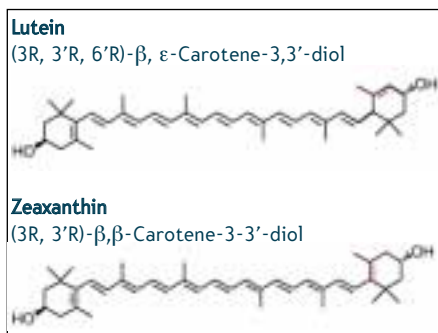
Light damage

Due to the absorption of practically all wavelengths less than 400nm by the lens, the effect of UV light on the macula is probably negligible²³. Indeed, there is no evidence in any human population that ultraviolet light exposure is related to ARM/AMD²³. Visible light, in contrast, may be aetiologically important for ARM/AMD. Noell has reported rod cell death following exposure to light of 500nm²⁴, and damage to RPE cells has been demonstrated following exposure to blue light (430nm)²⁵. The mechanism whereby visible light causes retinal damage is believed to relate to oxidative stress²⁶. In vitro studies agree that the retina is more vulnerable to damage by the blue portion of the visible spectrum than by any other wavelength.

Epidemiological studies investigating a link between cumulative exposure to light and the risk for ARM/AMD are numerous, and inconclusive. In brief, the cohort studies have shown an increased risk of ARM/AMD associated with cumulative exposure to light, whereas the case-control studies have not¹⁸.

Macular pigment (MP)

In the middle of the retina exists a depression called the fovea, where the cone photoreceptors reach their maximum density, and highest visual acuity is obtained⁴. The macula is a circular area 5-6mm in diameter, with the fovea at its centre, which lies within the vascular arcades of the retina²⁷ (Figure 1). Lutein



▶ **Figure 2**

Chemical structures of lutein and zeaxanthin
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and zeaxanthin accumulate in the macula to the exclusion of all other carotenoids, and are collectively referred to as macular pigment (MP). Human MP peaks at the centre of the fovea, and is optically undetectable outside of the macula but does exist in trace amounts in peripheral retina²⁸. The yellow colouration of the macula is attributable to the presence of MP²⁹.

Lutein and zeaxanthin are just two of more than 600 carotenoids found in nature³⁰. As can be seen in **Figure 2**, the difference between the two hydrocarbon structures is the position of the double bond in the six-carbon ring at the right. Therefore, lutein is an isomer of zeaxanthin. Both lutein and zeaxanthin are lipophilic substances which are among the class of carotenoids commonly referred to as the xanthophylls³¹.

Carotenoids are not synthesised *de novo* by animals³² and, therefore, MP is entirely of dietary origin. Food sources rich in lutein include dark, green leafy vegetables such as spinach, kale and collard greens³³. Sommerburg et al have shown that fruits and vegetables of various colours, such as green and orange peppers, as well as egg yolk, are also rich in the macular carotenoids³⁴. Hammond et al observed an increase in MP density within four weeks of dietary modification, consisting of increased intake of natural sources of L and Z, for most, but not all, subjects studied, indicating that the response to dietary carotenoids varies among individuals³⁵.

The function of MP remains uncertain, but it is known to reduce chromatic aberration¹⁸. Also, the absorption spectrum of MP peaks at 460nm (blue light), leading to speculation that it has a role in protecting the macula against the photo-oxidative effects of damaging blue light. Finally, L and Z are also believed to actively confer protection against oxidative stress by quenching free radicals¹⁸. The latter two properties have prompted speculation that MP may protect against ARM/AMD. This hypothesis is particularly provocative because MP is entirely of dietary origin.

Evidence for a protective effect of MP for ARM/AMD

Dietary intake and serum concentrations of L and Z

Some observational epidemiological studies have shown a reduced risk of ARM/AMD in subjects with a higher intake of lutein and zeaxanthin, or higher plasma concentrations of these compounds³⁶, while other epidemiological studies have failed to show such protective effects³⁷.

Risk factors for AMD

Age and advanced disease in the fellow eye are the two most important risk factors for ARM/AMD³⁸. Of the putative risk factors for ARM/AMD, some can be modified, and some cannot. Non-modifiable risk factors include female gender, family history, iris colour and hyperopia. Risk factors which, in theory at least, are subject to modification include cigarette smoking, physical inactivity, hypertension, cardiovascular disease, low dietary and blood carotenoids, raised serum cholesterol, low serum zinc, excessive alcohol consumption, and excessive lifetime exposure to sunlight³¹. However, the beneficial effects of risk factor modification remain unproven, and considerable debate persists regarding all the above putative risk factors.

Iris colour

Hammond et al have shown a significant and positive relationship between macular pigment density and iris pigmentation³⁹. The authors have put forward two possible explanations to account for their result, and its implication that a relative lack of MP is associated with increased risk of ARM/AMD. Firstly, they suggest that a shared tendency to accumulate melanin and retinal carotenoids might exist, as both mechanisms may have coevolved in response to environmental pressures such as light and oxygen. Secondly, macular pigment depletion may occur as a result of oxidative stress in eyes with light coloured irides because of increased light transmission⁴⁰.

Gender

Psychophysical studies have shown that individuals differ widely in optical density of their macular pigment, varying by up to a factor of 10. Although there is a lack of agreement on whether or not female sex is a risk factor for ARM⁴¹⁻⁴², many investigators have demonstrated that women are at greater risk of neovascular AMD than men^{41-43,8}. In 1996, Hammond et al reported that males had an average of 38% more macular pigment than females ($P < 0.001$) after adjusting for age and caloric intake⁴⁴. Furthermore, both sexes yielded a positive correlation between serum carotenoids and the density of macular pigment, but this relation was stronger in men (males $r = 0.62$; females

$r = 0.3$). The investigators suggested that the less robust relationships found between retinal, diet and blood carotenoids among females may be due to the presence of moderating variables and/or possible hormonal interactions.

In a Midwest population-based study, investigators reported no significant sex differences in either serum concentrations of L and Z or MPOD ($r = 0.21$, $P < 0.001$, and $r = 0.025$, $P < 0.001$, respectively), although females average intake of L and Z was greater⁴⁵.

Obesity

A recent study carried out by Hammond et al has shown that obese subjects tend to have lower retinal lutein and zeaxanthin⁴⁶. The authors speculated that this relative lack of MP is due to competition between adipose tissue and the retina for uptake of lutein and zeaxanthin, and/or decreased dietary intake of these carotenoids in obese individuals as reported elsewhere⁴⁴⁻⁴⁵. These findings lend themselves to further interpretations as females tend to have higher body fat than males, possibly explaining the predisposition of women to ARM/AMD.

Lens density

The lens and the macula both accumulate lutein and zeaxanthin to the exclusion of all other carotenoids in the blood⁴⁷. Liu and co-workers have hypothesised that ARM and age-related cataracts share a common pathogenesis⁴⁸, namely, oxidative stress. This hypothesis is consistent with reports that there is an increased cataract risk associated with tobacco use⁴⁹, light exposure⁵⁰⁻⁵¹ and inadequate intake of dietary antioxidants⁵²⁻⁵³. It has been postulated that persons with higher macular pigment density may also accumulate greater quantities of L and Z in the lens, thus protecting both organs⁴⁷. This hypothesis is consistent with Hammond et al's finding of an inverse relationship between macular pigment optical density and lens density ($r = 0.47$; $p < 0.001$)⁵⁴.

Age-related Eye Disease Study (AREDS)

The AREDS study is a multicentre prospective study of 4,757 individuals aged 55-80 years designed to assess the effect of dietary antioxidant supplements on the clinical course of ARM and cataract. The clinical trials were initiated largely because of the widespread public use of commercially available pharmacologic doses of vitamins and minerals to treat these two eye conditions, and the absence of definitive studies on the safety and efficacy of their use⁵⁵. Of note, when this study began in November 1992, L and Z were not commercially available in supplement form.

In brief, the results showed that a supplements of dietary antioxidants plus

zinc resulted in a reduced risk of progressing to visually consequential AMD by 25% in patients with extensive intermediate drusen, large drusen or non-central geographic atrophy in one or both eyes, or advanced AMD or visual acuity of 6/9 or worse in one eye due to AMD. These supplements consisted of 500mg of vitamin C, 400IU of vitamin E, 15mg of beta-carotene and 80mg of zinc daily, and this represents five to 15 times the recommended daily allowance of these antioxidants.

It is tempting to hypothesise, therefore, that the observed reduction in risk of progression to AMD would have been more dramatic if the locally relevant antioxidants had also been used in the form of L and Z, especially since antioxidants are known to work in a synergistic fashion.

Supplementation with L and Z

To date, there are no published studies which have investigated the putative benefits of L and Z supplements with respect to ARM or AMD. However, as these carotenoids are the most biologically relevant antioxidants for the health of the macula, and in view of the AREDS findings, the possibility that dietary carotenoids could delay, modify or even prevent ARM/AMD cannot be ignored. A randomised controlled clinical trial of supplemental L and Z, with and without co-antioxidants, is clearly needed, and should be supported.

The Waterford Study

To date, studies investigating MP and its relationship with ARM/AMD are limited for two main reasons. Firstly, they are observational in nature and secondly, most of the studies reported include relatively small numbers of subjects. On the basis of evidence currently available to us, firm conclusions cannot be drawn with respect to the risks and benefits of dietary supplements of L

and Z in the context of ARM/AMD.

In Waterford, in the Republic of Ireland, recruitment of 800 healthy volunteers is underway, in a study funded by Fighting Blindness, to establish the relationships between macular pigment optical density, serum concentrations of L and Z and dietary intake of these carotenoids. Analysis of the results will also examine whether a confirmed family history of ARM/AMD affects these relationships, or whether healthy subjects with high putative risk for the condition have less MP than individuals at no such risk.

Conclusion

The assumption that MP protects against AMD seems biologically credible, but remains unproven. This hypothesis requires longitudinal studies involving serial measurements of MP, and plasma lutein and zeaxanthin, in large numbers of subjects for it to be tested. Clinical trials investigating lutein and zeaxanthin supplements with respect to ARM progression are also required.

The possibility that a person's diet may be the key factor in the prevention, or delay in the onset, of this disease cannot be dismissed. Consequently, a balanced diet rich in fruit and vegetables should be encouraged for all people, particularly patients with ARM or AMD, or at risk at developing this disease.

About the authors

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References

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