Modifiable risk factors for age-related macular degeneration

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ABSTRACT

- Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in Australia and other Western countries.
- As there is no cure for AMD, and treatments to stop its progression have met with limited success, there is an interest in identifying modifiable risk factors to prevent or slow disease progression.
- To date, smoking is the only proven modifiable risk factor for AMD. Other factors under study include (i) cardiovascular risk factors such as hypertension, body mass index, and atherosclerosis; and (ii) dietary risk factors including fat and antioxidant intake, but so far these studies have produced conflicting results.
- Dietary fat in relation to AMD has recently attracted media attention. Despite very limited work supporting an association between vegetable fat and AMD, widespread publicity advocating margarine as a cause of AMD and encouraging use of butter instead has caused confusion and anxiety among sufferers of AMD and the general public, as well as concern among health professionals.
- The antioxidant carotenoids — lutein and zeaxanthin — found in dark green or yellow vegetables exist in high concentrations in the macula and are hypothesised to play a protective role. Of nine controlled trials of supplementation with carotenoids and other antioxidants, three suggested that various combinations of antioxidants and carotenoids were protective.
- While a low-fat diet rich in dark green and yellow vegetables is advocated in general, any specific recommendations regarding certain fats or antioxidant supplementation and AMD are not based on consistent findings at this stage.

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Age-related macular degeneration (AMD) is the leading cause of severe visual loss in our community, and is responsible for nearly half the cases of legal blindness in Australia.[1] It is a progressive, late-onset degenerative disease affecting central vision, which is essential for activities such as driving and reading. The resultant severe disability involves enormous personal costs and a massive burden on health resources. AMD is generally regarded as a complex genetic disorder with the added impact of environmental risk factors. To date, the pathogenesis of AMD remains unknown.

The prevalence of AMD increases exponentially with age (Box).[1] Australian data from the Visual Impairment Project and the Blue Mountains Eye Study predict that the number of people in Australia with AMD will double in the next 20 years, with direct costs to the community reaching over $1 billion by 2020.[2] Unfortunately, current treatment options for AMD have limited success, with even the newest treatments, such as photodynamic therapy and vascular endothelial growth factor (VEGF) inhibitors, applicable to only some cases, and lost vision is seldom regained.

Signs of early AMD are easily detected on fundus examination of the macula. Early AMD is usually not associated with loss of vision. The annual rate of progression to severe sight-threatening complications is around 5% for those with significant early disease. Vision loss in late AMD is characterised by neovascular disease, with growth of new blood vessels that leak underneath the central retina (wet AMD), or geographic atrophy in which an area of retina in the macula atrophies (dry AMD).

Better understanding of modifiable risk factors will allow us to identify and change at-risk behaviour, and implement preventive strategies early in the disease. To date, proven risk factors for AMD include age, family history and smoking, with smoking being the only modifiable risk factor.

Studies of modifiable risk factors

Cardiovascular risk factors and AMD

Smoking

Observational studies have revealed that AMD shares a number of overlapping risk factors with atherosclerosis, among which age[1] and cigarette smoking[1,3] have been most consistently demonstrated. A dose–response relationship has also been found between smoking and neovascular AMD.[4] A recent review confirmed that smoking was the most important and only agreed upon modifiable risk factor for AMD.[5]

Hypertension

Observational studies linking AMD to systemic hypertension have given conflicting results. A cohort study of 1828 subjects found that a longer duration of systemic hypertension was associated with a higher prevalence of early AMD.[6] Another large cross-sectional study found that AMD was associated with increased systolic blood pressure,[7] while a smaller study linked it to diastolic blood pressure.[8] A large case–control study by the Age Related Eye Disease Study group found a positive association between diastolic blood pressure, history of hypertension and use of antihypertensive medication, and wet AMD but not dry AMD.[9] However, several recent, large observational studies with over 4000 subjects failed to confirm any significant link between AMD and hypertension.[10,11]

Body mass index

There is also some evidence from observational studies linking AMD to body mass index. Results from several large studies have all shown a positive relationship between early AMD and high body mass index.[11-13] Waist-to-hip ratio has also been implicated in development of early AMD in women.[13]

Atherosclerosis

With regard to actual associations of AMD with atherosclerosis, the data have been inconsistent. Some observational studies have shown positive associations between AMD and atherosclerosis,[14,15] while others found a positive association between AMD and carotid artery atherosclerotic plaques.[15] Other large observational studies have found no such association.[10,11,16]

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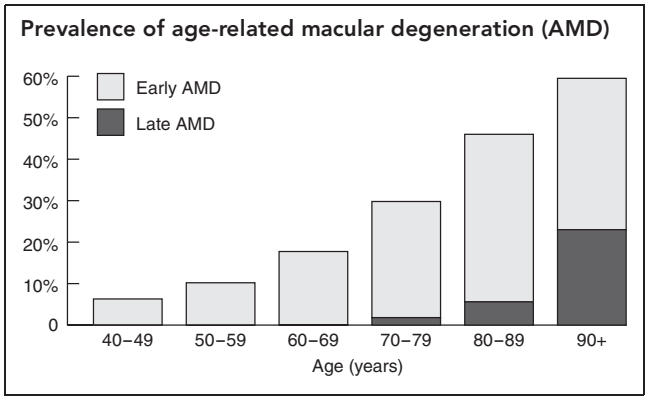

Cholesterol level

If the association between cardiovascular risk factors, cardiovascular disease (CVD) and AMD holds, then treatment of CVD itself could have an impact on AMD. Based on this rationale and theories about the possible benefits of the cholesterol-lowering statin family of drugs, the relationship between AMD and the use of statins has been examined in several clinical studies, with contradictory results.[17] However, these studies have been either cross-sectional or cohort studies relying largely on patient recall of the medications taken, and there have been no randomised controlled trials (RCTs) of statins in patients with AMD published to date. Thus, it is not clear whether statins have a protective effect in AMD.[18,19] An RCT using simvastatin (Merck Sharp & Dohme) is currently under way in Australia.[20]

Dietary risk factors and AMD

Dietary fats

Evidence of a possible role of fatty acids in AMD has come from several sources: links between cardiovascular disease and AMD; the association of a cholesterol pathway gene, the apolipoprotein E gene, with AMD; and the fact that the lipid content of the Bruch membrane — a semipermeable membrane that separates the photoreceptors from their blood supply — builds up exponentially with age.[21,22] The long-chain fatty acid, docosahexaenoic acid (DHA) is in high concentrations in the photoreceptor outer segments and is constantly shed and turned over during the normal visual cycle. A deficiency of DHA might therefore impair retinal function and promote AMD.[23] Thus, there is a particular interest in research into fatty acids and AMD.

More recently in Australia, there has been widespread media publicity of a possible association between vegetable fats or margarine and AMD. The evidence to support any association between AMD and dietary fat in general, or certain fatty acids in particular, is very limited and often conflicting. PubMed and MEDLINE searches from 1966 until October 2005 revealed only six observational studies evaluating dietary fats and AMD, with inconsistent results.

Results from two observational studies from the United States have led to recent controversial conclusions and recommendations regarding dietary fats. The first study, published in 2001, was a retrospective case–control study of 339 cases and 504 controls, suggesting that there was a higher risk of late AMD with higher vegetable fat intake (odds ratio [OR], 2.22; 95% CI, 1.32–3.74), and a lower risk with higher fish intake.[24] In 2003, the same team looked at progression of disease in a prospective cohort study of 261 patients with early AMD. After an average follow-up of 4.6 years, they found a significant association between total fat intake (relative risk [RR], 2.74; 95% CI, 1.10–6.62) and vegetable fat intake (RR, 2.43; 95% CI, 1.10–5.37) and a higher risk of AMD progression.[25] Higher saturated fat intake was also positively associated with AMD progression (RR, 1.96; 95% CI, 0.85–4.53), although this association was not statistically significant.

However, another US study, a 10-year retrospective population-based cohort study of 2429 participants, found an increased prevalence of AMD in those with the highest intake of saturated fats (mainly animal fats) (OR, 1.8; 95% CI, 1.2–2.7, *P* trend = 0.01). They also found the strongest association of increased risk of AMD in those with the highest butter intake (OR 1.5; 95% CI, 1.1–2.1, *P* trend = 0.006), although vegetable fats as a group were not investigated.[26]

Another 12-year pooled prospective cohort study of 72 489 participants revealed an increased risk of AMD in those with the highest intake of total fat (RR, 1.54; 95% CI, 1.17–2.01, *P* trend = 0.008); and a reduced risk of AMD in those with more servings of fish per week (RR, 0.65; 95% CI, 0.46–0.91, *P* trend = 0.009). However, the investigators did not find a statistically significant result for either animal fat (RR, 1.19; 95% CI, 0.87–1.62) or vegetable fat (RR, 1.33; 95% CI, 0.95–1.87) and the risk of AMD.[27]

The US studies on dietary fats need to be interpreted cautiously before applying them to an Australian diet. The increased risk associated with vegetable fats, reported in the articles by Seddon et al,[24,25] is postulated to be due to the high levels of *trans* fatty acids (TFAs) in US margarines.

TFAs are formed industrially when liquid unsaturated fatty acids are hardened through a process of partial hydrogenation. These partially hydrogenated fats remain solid at room temperature and are more resistant to oxidation and spoilage, so they have been commonly used in shortenings, some margarines, and industrial cooking oils. In the 1990s, in Australia, concern about TFAs' adverse effects on blood lipids led manufacturers to greatly reduce levels of TFAs in margarines. US margarines, on the other hand, still contain far greater quantities of TFAs.[28] Therefore, the results of US studies on dietary fat intake may not be applicable to other countries like Australia.

In the Australian Blue Mountains Eye Study, a cross-sectional population-based study, a borderline statistically significant increased risk of early AMD with higher total fat intake (OR, 1.6; *P* trend = 0.08) and monounsaturated fat intake (OR, 1.5; *P* trend = 0.05) was found. There was also an increased risk (OR, 2.7; *P* trend = 0.04) of late AMD with higher cholesterol intake (animal fat).[29] Although vegetable fats as a group were not investigated, they found polyunsaturated fats, which are derived mainly from vegetable fats, to be protective (OR, 0.4; *P* trend = 0.07) for late AMD. More recently, results from another Australian prospective cohort study found no relationship between polyunsaturated fats (vegetable fats) and incident cases of AMD, but found omega-3 fatty acids to be protective for early AMD (OR, 0.4; 95% CI, 0.2–0.8).[30]

Based on the limited data from the US, there has been publicity in Australia urging people to avoid vegetables oils, particularly margarine, arguing that they cause AMD and encouraging people to eat butter (a saturated animal fat) instead. With the limited, often conflicting, information regarding fats and the risk of AMD,

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there appear to be no grounds to support any such public health message at this stage. However, it still remains clear that saturated fats are the main dietary cause of high blood cholesterol levels, and groups promoting heart health strongly recommend limiting saturated fat intakes. Saturated fats are found in mainly animal fats and in some plant oils (coconut oil, palm oil, cocoa butter). This message is still particularly pertinent for people concerned about AMD, given the possible links between CVDs and AMD outlined above.

Thus, while it is desirable to advocate a public health message of a low-fat diet in general, a specific recommendation regarding certain fats and AMD is not based on consistent findings at this stage.

Antioxidants

The antioxidant carotenoids, lutein and zeaxanthin, found in dark green or yellow vegetables, exist naturally in high concentrations in the macula and have been proposed to play a protective role against the development of AMD.[31] While the exact protective role of these macular pigments remains uncertain, it has been hypothesised that they may limit the damaging photo-oxidative effects of blue light through its absorption, and, because of their antioxidant effects, protect against the adverse effects of photochemical reactions.[32] Aside from lutein and zeaxanthin, other antioxidants of interest include vitamins C and E, β-carotene, and the trace element zinc. PubMed and MEDLINE searches from 1966 until October 2005 revealed 23 observational studies and nine controlled trials evaluating dietary antioxidant intake (either individually or in combination) and the risk of AMD, with inconsistent results.

Of the nine controlled trials, three suggested that supplementation with various combinations of carotenoids and other antioxidants was protective. The largest and best conducted RCT from the Age Related Eye Disease Study (AREDS) group investigated the use of antioxidants (high doses of vitamin C, 500 mg; vitamin E, 400 IU; β-carotene, 15 mg) and zinc, 80 mg, with progression of AMD.[33] They followed up 3640 participants for an average of 6.3 years. They showed that the use of antioxidants and/or zinc in the 2577 participants with a high-risk of AMD (AREDS category 3 or 4) resulted in a reduced risk of disease progression of between 17% to 25% when compared with placebo, with the greatest risk reduction in those taking the combination of antioxidants and zinc. No benefit was seen in lower-risk AMD groups (AREDS category 1 or 2).

There has been much debate about the interpretation of the AREDS data and the appropriateness of the widespread use of this high-dose supplement. However, these data have been widely distributed to people at risk of visual loss from AMD. As increased risk of lung cancer among smokers taking β-carotene supplements[34,35] was noted during the study, the AREDS formulation is not recommended for smokers.

In Australia, the Macu-Vision supplement (Blackmores, Sydney, NSW), produced to mimic the AREDS formulation, excluded β-carotene due to the health risks. Though only one tablet is recommended on the bottle, two tablets need to be taken to achieve the same level of supplementation used in AREDS. In Australia, a recent study of 100 patients with high-risk AMD revealed that 38% were taking supplements, but only 1% of them were taking the correct dose.[36]

Among the other six trials which did not show any associations between zinc, vitamin E and other multivitamin intake with AMD, we will highlight two of the larger and better conducted trials: (1) VECAT (vitamin E, cataract, and age-related maculopathy trial), an RCT of 1193 participants randomised to 500 IU of vitamin E or placebo, revealed no benefit (RR, 1.05; 95% CI, 0.69–1.61) for early AMD.[37] (2) the ATBC (α-tocopherol and β-carotene) study, an RCT of 29 000 males randomly assigned to receive vitamin E 50 mg/day; β-carotene 20 mg/day; both vitamin E 50 mg/day; and β-carotene 20 mg/day; or placebo, from which a randomly selected sample of 941 participants from the original cohort underwent an ophthalmological examination, did not reveal beneficial effects from the 6 years of supplementation.[38]

The mechanism of protection by antioxidants remains a hypothesis only, and the side effects of the above supplements in high doses for extended periods of time remain unknown.

Conclusion

Identifying modifiable risk factors for AMD could have enormous implications for our ability to prevent visual loss from this devastating disease. It will allow us to target people for intervention and it will further our knowledge of the mechanisms causing this enigmatic disease, which in turn may lead to improved treatment.

However, to date, very little information on modifiable risk factors is consistent and well validated, such that the only agreed upon modifiable risk factor is smoking. Hence, all patients with signs of AMD should be strongly counselled to give up smoking. Advocating a low-fat diet and a diet rich in vegetables containing lutein, zeaxanthin and antioxidants would seem reasonable, as this is the basis of a healthy diet. Beyond this, other dietary and lifestyle recommendations require further validation before they are incorporated into public health advice.

Competing interests

None identified.

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