



Age-related macular disease

Part 3 - Risk factors for AMD



Dr Frank Eperjesi describes the modifiable and non-modifiable risk factors for age-related macular degeneration. **Module C8498**, one general CET point, suitable for optometrists and DOs

This article is the third and final in the series on age-related macular disease. The first article (October 19 2007) described the classification of this eye disease while the second (November 16 2007) reviewed techniques and equipment useful in the detection of wet age-related macular degeneration (AMD). This article will highlight some of the key risk factors associated with AMD. These can be divided into two groups – modifiable and non-modifiable. Further details of all risk factors for AMD can be found in Table 1. Risk factors supported by solid research evidence – specifically age, genetic predisposition, gender, race and iris colour along with smoking, alcohol, nutrition, no statin usage and sunlight exposure – are reviewed here.

TABLE 1
Non-modifiable and modifiable risk factors for age-related macular disease

Non-modifiable	Modifiable
Age	Smoking
Genetic predisposition	Alcohol
Gender	Socioeconomic factors
Race	Nutrition
Iris colour	Body mass index
Type I diabetes	Dietary fat intake
Refractive error	Cardiovascular disease
Cataract	Hypertension
Handgrip strength	No statin usage
Optic disc appearance	Aspirin
Size at birth	Type II diabetes
	Sunlight exposure
	Parity (child birth)

Non-modifiable risk factors

Age
Increasing age is considered to be the most important risk factor for AMD.¹ Reported prevalence ranges from 0.2 per cent of the population aged 55 to 64 years, 13 per cent in those older than 85 years² and up to 25 per cent in those aged 65 to 75 years.³ Geographic atrophy – sharply delineated round or oval area of hypopigmentation or apparent absence of the RPE in which choroidal vessels are more visible than in surrounding areas – among the population is reported to increase from 0.04 per cent in those aged between 55 and 64 years, to 4.2 per cent for those older than 85 years. Exudative AMD follows a similar pattern, 0.17 per cent in those aged 55 to 64 years and 5.8 per cent for those older than 85 years.⁴ An eight- to 10-fold increase in the prevalence of the condition has been recorded in those over the age of 90 years, compared with those aged 50 years.⁵

Genetic predisposition
A genetic basis for AMD is supported by the findings of several epidemiological studies.⁶ The complex aetiology of the disease has hindered the progress of

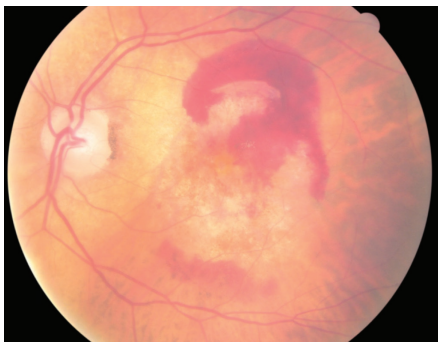
genetic studies, as it is a multifactorial disorder and is most probably controlled by more than one gene. An autosomal dominant pattern of inheritance has been reported in some patients,⁷ but no definitive genetic component has yet been identified. One study has suggested that approximately 25 per cent of AMD in the population might be attributed to a genetic component⁶ and another reported that family history is the strongest risk factor for the disease.⁸ First-degree relatives of patients with the condition have been reported to develop the disease at an increased rate and at a relatively younger age. Relatives of patients with age-related maculopathy (ARM) have a 50 per cent risk of developing the condition.⁶ In the Rotterdam Eye Study the children of subjects with AMD were 12 times more likely to develop the condition than children of subjects showing no signs of AMD.⁹ This relationship does not, however, exclude the possibility of an environmental influence.

Gender
The Beaver Dam Eye Study (BDES) found that, after adjusting for age, women of 75 years or more had

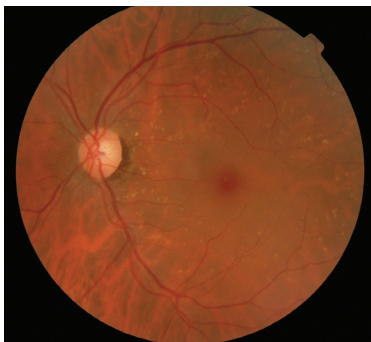
twice the incidence ARM, and more than seven times the incidence of AMD than men of the same age.⁴ One hypothesis for this increased risk is the loss of protective oestrogen in post-menopausal women. The Eye Disease Case-Control Study Group (EDCCS) reported a higher incidence of ARM in women who had given birth.¹⁰ Parity (number of children to which a woman has given birth) greater than one was associated with a 1.8 times increased risk of AMD in a case-control study.¹¹ Data from the Rotterdam Eye Study showed that women who had an early menopause following the removal of one or more ovaries had a significantly increased risk of developing AMD than women who had their menopause at 45 years or later.¹²

Race
Several studies have provided evidence to suggest that AMD is more common in whites than blacks. In the Baltimore Eye Survey¹³ AMD accounted for 30 per cent of bilateral blindness in whites and 0 per cent in blacks. AMD occurred in 2.1 per cent of the white population over 70 years, and no cases were detected among black subjects in this age group. Drusen were identified in 20 per cent of individuals in both racial groups, but larger drusen occurred in 15 per cent of whites compared with 9 per cent of blacks. Retinal pigmentary abnormalities were also more common among older whites, occurring in 7.9 per cent of white, and 0.4 per cent of black subjects.¹³ The Age-related Eye Disease Study (AREDS) found a greater risk of choroidal neovascularisation in whites than non-whites.¹⁴ However, AREDS investigators reported that the prevalence of ARM did not differ significantly between whites and blacks, 20.2 per cent and 19.8 per cent respectively.¹⁴

It has been hypothesised that racial differences could be related to melanin, which acting as a free radical scavenger, or in some other way, may protect the RPE, Bruch's membrane, choroid, or the outer retina from degenerative



Choroidal neovascular AMD



Early atrophic AMD changes

changes.¹⁵ The melanin acts as a ‘sink’ for short wavelength light and protects the retina, and in particular the macula, from oxidative damage.¹⁶

Iris colour

A number of studies have reported an increased risk of AMD in people with blue irises and light pigmented ocular fundi, compared with those with darker eyes. Blue iris colour has been significantly associated with an increased risk of ARM and AMD.¹⁶ It is thought that the lower risk of AMD in pigmented eyes is due to increased ocular melanin in the iris and choroid. However, other studies found no relationship between iris colour and AMD.¹⁷

Modifiable risk factors

Cigarette smoking

Smoking depresses serum antioxidant levels and is associated with alteration of choroidal blood flow. These mechanisms may be involved in the development of AMD.³² Men who smoke one pack of cigarettes per day have 72 per cent of the plasma antioxidant levels of non-smokers.³³ The reduced availability of antioxidant components may result in oxidative insult to the outer retina, leading to an increased risk of developing the condition. Furthermore, tobacco smoke is a vasoconstrictor and the damage it causes to choroidal blood vessels and blood flow may promote atherosclerotic and hypoxic changes in choroidal vessels.¹⁷ A greater number of cigarettes per day, a greater number of smoking years and lower ages at which smoking started are all associated with a higher risk of developing ARM.¹⁸ Another study found that subjects who were younger than 85 years and current smokers had a 6.6 times increased risk of exudative AMD compared with those who had never smoked.¹⁹ This increased risk remained in subjects who had stopped smoking less than 20 years before examination.²⁰

The risk of AMD has been shown to increase with longer duration of

smoking, with up to a five-fold increased risk among people who had smoked for 40 years or more.²⁰ These results provide evidence for a dose response relationship of lifetime exposure that reflects the duration and amount of current and past smoking with AMD.²⁰ Several small studies have shown no relationship between smoking and AMD.²¹

Alcohol

The first published findings of the National Health and Nutrition Examination Survey²² found that red wine was associated with lower risk of AMD, which may be related to the antioxidant properties of phenolic compounds within red wine.²³ In the BDES, consumption of beer was related to an increased risk of retinal pigmentation and exudative AMD.²⁴ Compared

with non-drinkers, high alcohol intake has positive association with AMD. Men and women in the highest category of wine intake – two or more glasses of wine per day – have been shown to have a two-fold increased risk. This positive association was shown to be strongest with white wine. A high spirits intake was also associated with a significantly increased risk in men and women.²⁵ The high correlation between smoking and drinking may contribute to the positive association between AMD and heavy drinking.²⁵ Several studies have found no relation between alcohol consumption and age-related macular disease.

Nutrition

It is hypothesised that people with low antioxidant levels may be more prone to oxidative damage of the retina and thus to AMD.²⁶ This hypothesis received support from another study that showed higher serum levels of antioxidant micronutrients, particularly carotenoids, to be protective against AMD. Subjects with the highest serum levels of carotenoids had a 43 per cent lower risk of developing advanced AMD, compared to those with lower levels.¹³

Recent studies have indicated that dietary changes implemented early in life have an important role in preventing and slowing the development of AMD.²⁷ Fruits and vegetables are rich sources of protective carotenoids, in particular beta-carotene, lutein and zeaxanthin.²⁸ People who consume fruits and vegetables, in particular dark, leafy greens, at least once a day have a significantly lower risk of AMD compared to those who consume such foods less than once per week. Spinach is a particularly rich source of lutein and zeaxanthin and its consumption is associated with an 86 per cent lower risk of developing AMD.²⁹

Three randomised controlled trials have been carried out to investigate the effect of nutritional supplements on the progression of age-related macular disease. The Visaline and ATBC trials^{30,31} found no relationship between supplementation and the development and progression of AMD. However, the AREDS, the largest of the three studies, found that a combination of high dose vitamin C, vitamin E, beta-carotene and zinc was moderately effective in preventing progression to advanced AMD. This effect was only seen in those subjects with extreme intermediate drusen, large drusen or non-central GA without advanced AMD.³² At present, people with AMD should be advised to follow dietary guidelines that promote



Smoking depresses serum antioxidant levels



Carotenoids have been shown in studies to offer protection against AMD progression



an increased consumption of fruit and vegetables.

Cardiovascular disease

A predisposition to CVD may affect blood circulation in the retina and contribute to the development of AMD.²⁵ The narrowing of the choriocapillaris caused by atherosclerosis may result in increased haemodynamic resistance and a decreased supply of nutrients and oxygen to the retina.²⁵ This contributes to the deterioration of the RPE, due to the development of ischaemia or the build up of waste products.¹³ Risk factors for CVD such as smoking, hypertension, high serum cholesterol levels and high body mass index have all been adversely linked to age-related macular disease. Some protective factors for CVD such as antioxidant vitamin intake³⁴ and postmenopausal hormone use have also been reported to provide protection.²⁵

Systemic hypertension

It has been suggested that the choroidal blood vessels are affected by hypertension, leading to an increased risk of signs of ARM and that the atherosclerotic process that affects the cardiovascular system may also affect the choroidal vasculature.³⁵

The BDES reported that higher pulse pressure was associated with a 30 per cent increase in the five-year incidence of AMD, and a 25 per cent increased progression of exudative AMD in persons aged 65 years or more.³⁶ The AMD Risk Factors Study Group found a relationship between exudative AMD and moderate to severe hypertension, particularly among patients being treated with antihypertensive medication such as diuretics and vasodilators. All of the findings relating hypertension to AMD were observed in patients with the exudative form of disease. Atrophic AMD was not found to be related to systemic hypertension.³⁷ No relationship between systemic hypertension and age-related macular disease was found in some studies.³⁸ Differences in selection criteria, number of subjects, location, or timescale between the studies may be responsible for the inconsistency between results. Individuals with moderate to severe hypertension have been identified as being at high risk for development of exudative AMD, and require careful monitoring and follow up.¹⁴

No use of statins

Atherosclerosis and abnormalities in lipid metabolism are associated with an increased risk of AMD.³⁹ Statins

can modify the lipid profile and help to lower the risk of coronary heart disease, and may even induce regression.⁴⁰ Among men and women aged 66 to 75 years not taking statins, 22 per cent showed signs of AMD, compared with only 4 per cent of treated participants.

There are two suggested mechanisms. Firstly, statins may prevent accumulation of deposits in Bruch's membrane, which is thought to occur with high concentrations of plasma cholesterol. Secondly, antioxidant properties of statins might protect the outer retina from oxidative damage.⁴⁰

The small sample size and cross-sectional design of this study was addressed in a case-control study where a significantly lower frequency of age-related macular disease was reported in statin users compared to non-users.⁴¹ Two studies investigating the effects of lipid lowering agents and hypocholesterolaemic medications, however, found no association with ARM.^{42,43}

Sunlight exposure

Individuals who have received excessive light exposure and have low levels of protective antioxidant nutrients may be particularly vulnerable to AMD. The BDES showed that the amount of

outdoor leisure time was significantly associated with the development of ARM. Outdoor leisure time during teenage years (13 to 19 years old) and in the 30s has been significantly associated with the risk of ARM, and five or more daily outdoor hours has been shown to double the chance of developing ARM compared with two daily outdoor hours. A slight, but significant protective effect was associated with the use of hats and sunglasses during the teens and 30s.⁴⁴ The Pathologies Oculaires Liées à l'Age (POLA) Study found a reduced risk of soft drusen with use of sunglasses.⁴⁵

The Chesapeake Bay Study concluded that cumulative exposure to blue light or all wavelengths of light during the 20 years previous to examination was associated with an increased prevalence of AMD.⁴⁶ Several studies, however, found no such relationship.³⁸

References

A full list of references is available from the clinical editor: william.harvey@rbi.co.uk

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MULTIPLE-CHOICE QUESTIONS - take part at opticianonline.net

1 The increased risk of ARM in women may be related to:

- A Loss of protective oestrogen in post menopausal women
- B Parity
- C Early menopause
- D All of the above

2 Smoking:

- A Depresses serum antioxidant levels
- B Increases serum antioxidant levels
- C Has no effect on serum antioxidant levels
- D Increases serum carotenoid levels

3 Which of the following statements is true?

- A Red wine has been associated with a greater risk of AMD than white
- B Consuming two or more glasses of wine per day has been shown to increase the risk of developing AMD by three times
- C Heavy drinking is associated with reduced oxidative stress
- D The phenolic compounds in red wine may have antioxidant properties

4 In the Beaver Dam Eye Study, consumption of beer was:

- A Not related to exudative AMD
- B Not related to non-exudative AMD
- C Related to decreased retinal pigmentation
- D Not related to exudative or non-exudative AMD

5 Statin treatment:

- A May lower Bruch's membrane deposits
- B Increases choroidal blood flow
- C Reduces cholesterol deposits in the retinal nerve fibre layer
- D Causes oxidative stress in the outer retinal layer

6 Long-term exposure to blue light is thought to:

- A Increase prevalence of AMD
- B Be associated with reduced risk of soft drusen
- C Protect against ARM
- D Negate the need for sunglasses

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