Modifiable Risk Factors of Age-Related Macular Degeneration

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Key Points

- The causative factors for AMD have not been elucidated, but disease development is likely a combined result of gene vulnerability interacting with predisposing and often modifiable risk factors.
- Many studies have linked AMD to the effects of oxidative stress. Several of the risk factors discussed below are thought to further increase oxidative damage and/or limit the retina's ability to repair.
- While inferences can be made about the effect of many of these modifiable risk factors, additional studies are necessary before definitive recommendations are possible.

Pearl

Thornton's criteria for causal attribution when evaluating risk factors:

- Consistency of findings: between study types, settings, populations and time
- Strength of association
- Evidence of dose–response: greater intensity and/or duration of smoking associated with greater effect
- Evidence of reversibility: reduced risk with removal of exposure (i.e., among ex-smokers compared with current smokers)
- Temporal relationship: evidence that exposure preceded effect
- Biological plausibility: evidence of supporting biological evidence from animal and tissue models or other sources

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Introduction

Age-related macular degeneration (AMD) is a chronic progressive disorder characterized by drusen in the early stages and atrophy and/or choroidal neovascularization in the late stages. It is a leading cause of blindness in the elderly white population and carries a large individual and social burden.

Risk factors for AMD are numerous and multiple studies have been designed to identify and assess them (Table 2.1) [1]. The most consistently significant, yet nonmodifiable, factors are genetic predisposition and age. Multiple chromosomal susceptibility loci are currently being studied and are discussed elsewhere in this book.

Table 2.1 Risk factors for age related maculopathy

Genetic predisposition
Family history of ARM
Complement factor H gene
Apolipoprotein E gene
LOC gene
Cardiovascular disease
Clinical evidence of atherosclerosis
Angina/heart attack/stroke
Subclinical evidence of atherosclerosis
Carotid atherosclerosis
Aortic atherosclerosis
Cigarette smoking
Diabetes mellitus
Hypertension and associated disease
Ischemic cerebral white matter changes
Abnormalities of the retinal vasculature
Cholesterol
Total cholesterol
Low-density Lipoprotein (LDL) cholesterol
High-density Lipoprotein (HDL) cholesterol
Obesity
Female sex hormones
Endogenous estrogen exposure
Age at menarche
Age at menopause
Number of pregnancies
Exogenous estrogen exposure
Oral contraceptives
Hormone replacement therapy
Novel risk factors for atherosclerosis
Lipid-related factors
Apolipoproteins
Lipoproteins
Inflammatory markers
C-reactive protein
Interleukins
Serum amyloid A
Vascular and cellular adhesion molecules
Homocysteine/folate/vitamin B12/vitamin B6
Infectious agents
Cytomegalovirus
Helicobacter pylori
Chlamydia pneumoniae
Systemic diseases with inflammatory components
Gout
Emphysema
Anti-inflammatory medications
NSAIDs
Steroids
Markers of systemic inflammation
White blood cell count
Serum albumin
Plasma fibrinogen
C-reactive protein
Complement factor H Y402H polymorphism
CRP haplotype
Interleukin-6
Tumor necrosis factor-α
Markers of endothelial dysfunction
Intercellular adhesion Molecule-1
E-selectin
Indicators of oxidative stress
Anti-oxidants
Vitamin C
Vitamin E
Vitamin A
Carotenoids
Lutein
Zeaxanthin
α- and β-carotene
β-cryptoxanthin
Lycopene
Enzymes
Plasma glutathione peroxidase
Superoxide dismutase
Trace elements
Zinc
Pro-oxidant status

(continued)

Table 2.1 (continued)

Dietary fat intake
Total fat
Saturated fat
Polyunsaturated fat
Fish/fish oils
Visible light exposure
Sunlight/blue light
Ultraviolet-B
Ocular factors
Refractive error
Emmetropia
Myopia
Hypermetropia
Iris Color
Cataract
Nuclear sclerosis
Cortical lens opacities
Posterior subcapsular cataracts
Cataract surgery
Miscellaneous factors
Alcohol consumption
Beer
Wine
Spirits
Medication use
Estrogens
Lipid-lowering agents
CNS medications
Anti-hypertensive medications
Coffee consumption
Frailty
Physical activity

From Connell et al. [1], used with permission

Advancements are being made in locating others, but ultimately disease development is likely a combined result of gene vulnerability interacting with predisposing risk factors. As such the identification and management of modifiable risk factors is of particular epidemiological interest in the control of this disease.

Possible modifiable risk factors for AMD include smoking, body mass index (BMI), cumulative sunlight exposure, diet, alcohol consumption, and cardiovascular disease. Of these, diet and nutritional supplements have been the focus of many multi-center trials. The recommendations regarding the impact of micronutrients such as AREDS and AREDS-like supplements as well as carotenoids and omega fatty acids among others are covered in detail in this book in Chapter 5. Here, we will discuss the background and the emerging data that point toward some of the other modifiable risk factors.

Although still unproven, many studies have linked AMD to the effects of oxidative stress in the macula [2]. The naturally increased oxygen consumption from the photoreceptors combined with the lack of autoregulatory capacity of the choriocapillaris to increased metabolic demand and the decreased choroidal blood flow due to diminished vessel volume and density that occurs with age contributes to an increased formation of oxygen free-radicals and inflammatory response that promotes degenerative changes [3]. Several of the risk factors discussed below are thought to further increase oxidative damage and/or limit the retina's ability to repair [4].

Smoking

Smoking has been shown to be one of the strongest environmental risk factors for AMD. Current smokers tend to have a fourfold higher risk of 5-year incident advanced AMD than never smokers. Past smokers have a threefold higher risk of geographic atrophy [5]. Long-term longitudinal studies demonstrated that exposure to smoking precedes the development of AMD and that there is a dose–response: the risk of developing AMD increases as the intensity of smoking increases [6]. Smoking cessation was associated with a marked, nonlinear decrease of the risk of progression to AMD. This protective effect was independent of smoking intensity [7]. Recent studies have shown that the presence of certain gene polymorphisms, specifically complement factor H (CFH) gene, Y402H and LOC387715 A69S genes influence the effect of smoking on AMD development [8]. It is expected that other gene and smoking interactions will be discovered as the field progresses. Therefore, it is reasonable to advise all smokers of their increased prospect of AMD development.

Pearl

Smoking has been shown to be one of the strongest risk factors for AMD.

- Current smokers have a fourfold higher risk of late AMD than never smokers.
- Past smokers have a threefold higher risk for geographic atrophy.
- Ever smokers (past or present) have on average a 30% increased risk of either exudative or nonexudative AMD.
- Smoking cessation decreases the risk of AMD progression, albeit nonlinearly.

Alcohol

The epidemiologic data on the association of AMD with alcohol consumption is inconsistent [9]. In the Beaver Dam Eye Study, there was an association with retinal drusen in men and beer drinking (seven drinks per week), but none in women [10]. In the Blue Mountains Eye Study, there was no association found, and in the National Health and Nutrition Examination Survey I, wine consumption was reported to be protective leading to a 34% reduction in relative risk. The authors of that report speculated that antioxidant phenolic compounds found in high concentrations in red wine may explain their finding [8]. However, it similarly has been shown to increase oxidative stress or to modify the mechanisms that protect against oxidative stress, so it is hypothesized that alcohol may have a J-shaped effect on AMD risk: protective for AMD when consumed in moderate amounts and associated with an increased risk with heavier consumption. Further studies are necessary to allow for a recommendation, but results are hampered by the lack of a widely accepted definition of heavy or moderate alcohol use. Low-risk recommendations vary between less than 10–60 g/day among developed nations [9].

Increased Light Exposure

Macular pigments are thought to filter out damaging blue light and act as an antioxidant by quenching reactive oxygen species [11]. Light exposure, specifically blue light, bright sunlight, and ultraviolet (UV) radiation, has been implicated in photochemical oxidative damage and light-induced apoptosis of the RPE cells [5, 8]. Clinical studies have had difficulty quantifying light exposures. Some suggest that the use of hats and sunglasses from an early age may be slightly protective, but others show no statistically significant effect and no definite conclusion on the protective effect of modern filtering lenses can be made [12, 13]. On the other hand, it is known that the anterior structures of the eye, such as the cornea and the lens, filter UV light but allow visible blue light to reach the retina [11]. An association of cataract surgery and subsequent onset and progression AMD exists, but has not been statistically proven; a protective effect of cataracts has been postulated and attributed to additional filtering of blue light by the opaque lens [14]. Based on this, prophylactic ‘yellow’ intraocular lenses (IOLs) have been introduced and although indications for their use are not clear, theoretically they should be considered in patients at risk [15]. Additional clinical trials would be needed to prove this assumption.

Obesity

The relationship between obesity and AMD is also inconsistent. Most studies have examined AMD associations with weight parameters defined by the BMI (calculated as weight in kilograms divided by height in meters squared). Some have found no association while others found associations within specific population subgroups [16]. The waist to hip ratio (WHR), however, is a measure of central or abdominal obesity that is emerging as a better predictor of

diabetes and cardiovascular diseases than the BMI. Early studies also suggest that a reduction in WHR in middle-aged persons may be associated with a decrease in the likelihood of prevalent AMD [17]. With increasing rates of obesity in developed countries, future studies are needed to assess the additional benefit of weight loss in patients at risk of AMD.

Pearl

Calculating WHR (Waist to Hip Ratio)

- Measure around the hips where at their widest, then measure the waist around the largest part of the belly.
- Divide the waist measurement by the hip measurement to get the WHR
- Normal values range from 0.7 to 0.85 for women and 0.9 to 1 for men

Calculating BMI (Body Mass Index)

- Divide the weight taken in kilograms by the square of the height taken in meters.
- Bellow 18.5 is considered underweight
- 18.5–24.9 is within normal
- 25–29.9 is considered overweight
- >30 is considered obese

Exercise

Studies show that higher doses of physical activity correlate to lower incidence of exudative AMD [18]. In the Beaver Dam Eye study, persons with an active lifestyle (defined as regular activity three or more times a week) were found 70% less likely to develop neovascular AMD; an increased number of blocks walked per day decreased the risk of exudative AMD by 30% [19]. This is consistent with findings from the Eye Disease Case Control Study in which neovascular AMD was associated with less physical activity. However, physical activity has not been related to the incidence of early AMD or geographic atrophy. The benefits on exudative AMD may be the result of lowering systolic blood pressure, lowering white blood cell count, and decreasing BMI, factors found to be associated with neovascularization. Although at this time it is difficult to recommend specific activities, it seems that more general physical activity would be beneficial to patients at risk [8].

Dietary Fat Intake

Dietary fats can be divided into "bad" fats such as cholesterol, monounsaturated and polyunsaturated fats, and linoleic acid and "good" fats such as omega-3 and omega-6 monounsaturated fatty acids, the benefits of which are discussed in detail elsewhere in this book. There is a growing body of evidence suggesting that diets high in bad fats, rather than total fat intake, may contribute to the risk of intermediate and advanced AMD and that diets high in good fats may be protective [20, 21]. Proposed mechanisms for this increased risk include progressive accumulation of lipids in Bruch's membrane, atherosclerosis causing hemodynamic changes in the retinal and choroidal blood supply, and the depletion of omega-3 fatty acids and high serum levels of polyunsaturated fatty acids that cause oxidative damage to the retina. Given the overall health benefits found for a diet low in cholesterol and saturated fats, it is reasonable to consider it as well in this population [5].

Phytochemicals

Phytochemicals or phytonutrients are active plant compounds that are thought to have health-protecting qualities. While the antioxidant, immune-boosting, and other health-promoting properties of a number of compounds are being studied, the most publicized phytochemicals have been vitamin C, vitamin E, and beta-carotene (which the body converts into vitamin A); their antioxidant properties are covered in detail in the review of the AREDS studies elsewhere in this book. However, data has been

Fig. 2.1 Gingko biloba (From: http://upload.wikimedia.org/wikipedia/commons/2/2a/Ginkgo_biloba_leaf_3.jpg)

generally inconsistent, particularly concerning their relationship to AMD, because it is difficult to control other influencing lifestyle choices [22]. A few of the more commonly known compounds are reviewed here.

Ginkgo Biloba

Ginkgo biloba is one of the oldest living tree species (Fig. 2.1). Its leaves contain flavonoid glycosides that have been studied for their role in reduction of platelet aggregation, increased vasodilatation, and quenching of free radicals – the latter of which has sparked interest for its use on AMD. To date, there are no studies that demonstrate a definite positive effect on AMD, but also there have been few reports of toxicity, although it can increase the risk of bleeding in anticoagulated patients. Clinical trials have used between 120 and 240 mg daily [23, 24]. Dietary supplements generally provide 40–80 mg in a single dose.

Anthocyanins

Anthocyanins, also known as berry extracts, are water-soluble flavonoid pigments found in fruit such as blueberries, cranberries, bilberries, blackberries, blackcurrants, red currants, cherries, and purple grapes among others (Fig. 2.2). They act as potent antioxidants and are thought to reduce inflammation, aging, neurological diseases, cancer, and diabetes. In the retina, they are thought to inhibit photo oxidation and membrane permeability changes that can lead to AMD [23].

Fig. 2.2 Blueberries (From: http://upload.wikimedia.org/wikipedia/commons/7/7e/Blueberries_on_branch.jpg)

Fig. 2.3 Red wine (From: http://commons.wikimedia.org/wiki/File:Red_wine_closeup_in_glass.jpg)

Resveratrol

Resveratrol is a polyphenolic antioxidant found in red wine that appears to have antiinflammatory antioxidant and antiproliferative benefits (Fig. 2.3). Treatment with 50 and 100 μmol/L resveratrol has recently been shown to have significantly reduced in vitro the proliferation of retinal pigment epithelium cells by 10–25%, respectively, and as such is a compound of interest for ongoing studies [25].

Fig. 2.4 Green tea (From: http://flickr.com/photos/barnkim/932910717/)

Epigallocatechin Gallate

Epigallocatechin gallate (EGCG) is the principal flavonoid present in green tea (Fig. 2.4). It has powerful antioxidant abilities and, in the eye is thought to confer neuroprotection of retinas injured by ischemia and reperfusion. It has also been shown to be an effective inhibitor of RPE cell migration and adhesion to fibronectin and its role in AMD prevention is being explored [26, 27].

Pearl

Phytochemicals are increasingly studied for the following possible effects:

- As antioxidants
- In enzyme stimulation
- Hormonal action
- Antibacterial properties

Mineral Supplements

Several metals and minerals play a significant role in the visual cycle and photoreceptor survival. Zinc and copper are cofactors and are major constituents in several important enzymes. The AREDS study showed a reduction in the development of advanced AMD as well as a decrease in the rate of progression of intermediate AMD to advance AMD [28]. Selenium activates the antioxidant enzyme glutathione peroxidase, which protects cell membranes from oxidative damage [22].

Summary

The retina is the most metabolically active tissue of the body. Its high rate of oxygen consumption puts it at risk for increased oxidative damage, which is further aggravated by environmental and aging processes. In genetically susceptible individuals, this can lead to degenerative changes of the RPE and age-related macular degeneration. While current treatment modalities aim to stabilize vision and select patients do gain visual acuity, identification of preventable risk factors and behavior modification remain critical for best long-term visual prognosis.

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