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Managing patients at risk for age-related macular degeneration: a Canadian strategy

ABSTRACT

Background: To develop a consensus strategy for the management of patients at risk for age-related macular degeneration (AMD) for Canadian ophthalmologists, optometrists and physicians.

Methods: Development of a consensus strategy began with a review of the literature and existing guidelines. A panel of retina specialists, ophthalmologists, and optometrists from across Canada assessed this evidence to distill what was learned and use this knowledge as the basis for developing a consensus strategy for managing patients at risk of AMD.

Results: The expert panel has developed a series of recommendations for Canadian eyecare providers (eg. ophthalmologists, optometrists) and physicians to adopt as a preventive strategy for patients at risk of AMD.

Interpretation: This consensus strategy is a practical guideline that can be adopted in the office setting to manage patients at risk of AMD and to advise patients with questions and concerns about AMD.

Age-related macular degeneration (AMD) is an incurable, degenerative disease and the leading cause of blindness in adults >50 years in developed countries.¹ It has an appreciable socioeconomic impact that will only increase as our population ages, unless a way is found to prevent AMD or halt its progression.

There are two major types of AMD. Neovascular, also called “exudative” and “wet”, AMD is characterized by the development of choroidal neovascular membranes, subretinal hemorrhage and/or fluid, and fibrosis at the advanced stage. The more common form, dry and atrophic, accounts for about 85% of AMD. It is characterized by drusen and/or retinal pigment epithelial irregularities, often progressing to atrophic areas.² A small percentage of dry AMD progresses to neovascular AMD.²

AMD has a complex natural history that is poorly understood, although various risk factors have been identified. There is no cure for AMD, but current developments have made the management of AMD increasingly possible. Furthermore, insights into prevention and risk factors have aided the development of other important management strategies.

In 2007, in Toronto, an expert panel of Canadian ophthalmologists and optometrists met with several objectives:

- to understand the current best practices in managing patients at risk for AMD;
- to understand the current challenges in helping patients at risk in order to reduce the incidence of this debilitating disease and prevent its progression to advanced stages;
- to develop practical guidelines to help to prevent the progression of AMD in at-risk patients.

The purpose of presentations and subsequent discussions at this meeting was to supply background, perspective, and information from the existing literature and clinical practice to serve as a basis for the definition of a consensus strategy for the management of people at risk for AMD.

Incidence and Prevalence of AMD

No specific figures are available for the prevalence of AMD in Canada; however, it is not unreasonable to extrapolate from an important U.S. initiative: the Beaver Dam Eye Study. During the first study (1988–1990), Klein et al³ determined that signs of age-related maculopathy were present in 8.5% of people from 43 to 54 years and most common among people ≥ 75 years (36.8%). In the next study (2003–2005), Klein et al⁴ reported that the 15-year cumulative incidence of early AMD was 14.3% in adults > 43 years; for late AMD, it was 3.1%. Among people ≥ 75 years, the 15-year cumulative incidence of late AMD was 8%. Extrapolating the initial findings of the Beaver Eye Dam Study to the Canadian population determines that nearly

2.2 million Canadians may have some stage of AMD (Table 1).

With a decreasing birth rate and increasing life expectancy, the proportion of older Canadian adults is increasing more rapidly than other age groups.⁵ In 2005, the number of Canadian seniors (> 65 years) was projected to increase from 4.2 million to 9.8 million in 2036, almost doubling the percentage of seniors in the Canadian population from 13.2% to 24.5%.⁵

Burden of Illness

Brown et al⁶ reported that even a mild case of AMD (20/20 to 20/40 in the better-seeing eye) lessens quality of life for the average patient by 17%, similar to the impact of moderate cardiac angina or symptomatic HIV. Moderate AMD (20/50 to 20/100 in the better-seeing eye) causes a 32% decrease in quality of life, similar to the impact of severe cardiac angina or a fractured hip. Severe AMD ($\leq 20/200$ in the better-seeing eye) decreases quality of life by 53%, which is a greater impact than kidney dialysis. Those with very severe AMD ($\leq 20/800$ in the better-seeing eye) reported a 60% decrease in quality of life, similar to the impact of end-stage prostate

cancer or a catastrophic stroke. Of interest, Brown et al⁶ also reported that ophthalmologists dramatically underestimated the quality of life of patients with moderate and severe AMD.

These authors also reported that wet and dry AMD have an annual negative impact of approximately U.S.\$30 billion on the U.S. gross domestic product.⁶ A more recent economic analysis has estimated the indirect cost of wet AMD as U.S.\$2.5 billion per year in lost productivity.⁷ For dry AMD, indirect costs are measured at U.S.\$24.4 billion.⁷

Pathogenesis of AMD

The pathogenesis of AMD is multifactorial, involving genetic and environmental factors. It is associated with interactions in several biological processes, including oxidative stress and inflammation, leading to dysfunction of the retinal pigment epithelium (RPE), Bruchs membrane, and photoreceptor complex. Activation of these processes initiates a chain of events (Figure 1), manifested by the hallmarks of AMD:⁴

- Large numbers of small hard drusen appear between the RPE, Bruchs membrane, and the choroid.

- The drusen become larger and more confluent (“softer”). Pigmentary abnormalities (hyperpigmentation and atrophy) occur and lipofuscin increases in the RPE.
- Over time, central geographic atrophy of the RPE and/or angiogenesis may follow.

Oxidative stress and antioxidants

The RPE is a monolayer of unique cells that manages the flow of nutrients to photoreceptors, digests waste (outer rod and cone segments) from photoreceptors, and controls metabolism for the retina.⁸ The retina has high concentrations of oxygen, polyunsaturated fatty acids, and photosensitizers. These substances, combined with light exposure, make the retina susceptible to oxidative stress.⁹ How this works precisely is unknown, but one theory suggests that, as the rate of digestion of outer rod and cone segments decreases within the RPE, lipofuscin formation increases.

A recent study, which found oxidized phospholipids in photoreceptors and RPE cells, reported that the amount of these phospholipids increased with age.¹⁰ They also

found that eyes with AMD were more intensely immunoreactive for oxidized phospholipids than age-matched normal eyes. They concluded that oxidative damage to photoreceptors and RPE cells may be the mechanism for these changes. This conclusion was reinforced by Kamei et al¹¹, who found that macrophages and RPE express cell surface scavenger receptors for oxidized lipoproteins. These studies noted that the pathophysiology of AMD has some similarities to that of atherosclerosis, but the ramifications of this hypothesis have yet to be fully explored.

Oxidative stress can be exacerbated by external factors, particularly smoking and perhaps excessive sunlight exposure.^{9,12-14} Low levels of antioxidants and minerals upset the natural balance that normally neutralizes free radicals. Free-radical formation appears to impair the RPE’s ability to function properly. In the macula, a healthy RPE contains high concentrations of natural antioxidants, such as vitamin C, glutathione, vitamin E, retinoids, carotenoids, and enzymes, such as superoxide dismutase and phospholipid hydroperoxide glutathione peroxidase (PHGPx). In diets

with a low antioxidant intake, providing adequate antioxidant supplementation could be a key line of defence.

Specific nutrients in AMD

The benefits of nutritional supplementation in AMD are rooted in the AREDS trial.^{12,15,16} In this trial, high doses of Vitamins C and E, zinc, and beta-carotene have shown a benefit in retarding the progression of AMD in patients with moderate to advanced disease.

Lutein and zeaxanthin were not available at the time of the first AREDS trial, so definitive conclusions as to their benefits are still unknown. Both lutein and zeaxanthin, which give the macula a yellow colour, play a protective role as antioxidants and filter short-wavelength light. Various studies suggest a benefit for these carotenoids in the treatment of AMD. Observational data from the AREDS 22,¹⁶ Blue Mountain Eye Study,¹⁷ CAREDS,¹⁸ and POLA¹⁹ studies have associated a higher dietary intake of carotenoids with a lower incidence of AMD progression. Furthermore, Seddon et al²⁰ have shown that patients taking 5.8 mg/day of lutein had a 43% lower risk of wet

AMD. AREDS-2 will further define the role of these carotenoids in a randomized, controlled trial.

There is a suggestion that vitamin supplementation may help in the primary prevention of incident AMD. Van Leeuwen et al have specifically established their ability to protect against AMD, finding that “a high dietary intake of beta carotene, vitamins C and E, and zinc together was associated with a substantially reduced risk of AMD in elderly persons.”⁹

This statement seems to contradict a recent meta-analysis in the *British Medical Journal*, which reported the individual effects of dietary antioxidants on primary prevention of AMD.²¹ It concluded that, individually, insufficient evidence supports the role of dietary antioxidants, including the use of dietary antioxidant supplements, for the primary prevention of early AMD. One limitation of this meta-analysis, which the authors noted, is that they did not look at the effects of antioxidants in combination.

The Rotterdam Study, a prospective cohort study, has compared the effects of antioxidants individually and in combination. It reported that the results for individual antioxidants were not as strong as

the benefit reported when all four antioxidant supplements were taken together.⁹ This finding was similar to the AREDS trial, which reported significant reductions in the risk of progression to advanced AMD in the antioxidant arm (17%), zinc arm (21%), and antioxidant plus zinc arm (25% after 6.3 years and 27% in the 10-year extension).¹⁵ Perhaps benefits in both studies are attributable to the synergistic effects of antioxidants taken in combination rather than isolation.

Another limitation of the meta-analysis is that a large portion of the study population worked in the healthcare industry and therefore may not be indicative of the normal population.²¹

Risk factors

Precisely how the pathological process in AMD is initiated and progresses is not fully understood, but several risk factors have been identified. They are divisible into two groups: unmodifiable and modifiable.

Unmodifiable risk factors

Age: The Beaver Dam Eye Study, among others, has established that the incidence and the severity of AMD increase with age.⁴

Genetics: Based on twin and family studies, there appears to be strong evidence for a genetic component in the risk of developing AMD.^{2,22} Recent genome-wide linkage and association studies have focused on finding candidate genes for AMD. Among the loci of interest are 1q32 (complement factor H gene) and a region of 10q26 (LOC387715). Although the exact mechanism of how these single nucleotide polymorphisms lead to AMD is unknown, they appear to play a part in the inflammatory cascade and oxidative stress models of injury, respectively.²³

Gender: Women are at slightly higher risk of having one or more intermediate drusen, extensive small drusen, or RPE pigmentary abnormalities.¹²

Race: AREDS 3 found a higher frequency of choroidal neovascularization among Caucasians, who had a higher frequency of one or more large drusen (>125 µm) and extensive intermediate drusen.¹² The authors speculated that increased melanin in RPE cells, acting as a free radical scavenger or simply as a filter for ultraviolet radiation, protects the RPE cells and

Bruchs membrane, reducing the risk of developing large drusen and RPE pigmentary changes and therefore reducing the risk of geographic atrophy, choroidal neovascularization, or both.¹²

Eye colour: Hyman et al²⁴ found that brown eye colour was associated with less AMD. Frank et al²⁵ concluded that Caucasians with light-coloured irides have a higher prevalence of AMD than people with darker coloured irides.

Concurrent conditions: AREDS investigators found a correlation between AMD and concurrent conditions, such as hyperopia,¹² diabetes,²⁶ and a history of cardiovascular disease.²⁶

Modifiable risk factors

Smoking: Of all modifiable risk factors, smoking is the most important. AREDS 3 and 19 found that smoking was associated with more severe cases of AMD (wet and dry).^{12,20} The exact mechanism of damage is unknown, but AREDS 3 authors noted that smoking lowers levels of circulating antioxidants.¹² They proposed an underlying vascular basis for AMD, because smoking may damage choroidal vessels and

alter choroidal blood flow, thus promoting atherosclerotic and hypoxic changes in the choroidal vessels. Smoking may directly cause vasoconstriction, increasing hypoxia and oxidative stress.¹²

Lifestyle factors: Lifestyle factors, such as diet, fitness, obesity, and socioeconomic factors, play a role in AMD.²⁰

Sunlight: Another modifiable risk factor is exposure to ultraviolet solar radiation. Although evidence for the pathogenic role of sunlight exposure in AMD is controversial, it cannot be ignored.^{9,13,14}

Consensus

- AMD is a multifactorial disease. The relative impact of environmental and genetic risk factors is unknown.
- Many risk factors for AMD are well known, as shown in the medical literature.
- There is a lack of clinical evidence to show that management of risk factors can prevent the progression of early AMD. Randomized controlled trials, such as AREDS, have not made any conclusive recommendations for patients with early (category 1 or 2) AMD.

- Randomized clinical trials, such as AREDS, have shown that the management of modifiable risk factors has an impact on advanced AMD. For patients with category 3 or 4 AMD, the standard of care includes the management of modifiable risk factors.
- Despite evidence from randomized controlled trials, many people remain unconvinced about the importance of risk-factor management.
- Unmodifiable risk factors, such as age, genetics, gender, race, eye colour, and concurrent conditions, continue to be studied.
- The importance of modifiable risk factors, such as smoking, nutrition (including antioxidants, such as vitamin C, E, lutein, beta carotene, zeaxanthin, and zinc), lifestyle factors, and sunlight exposure need to be reinforced for patient awareness.
- The educational role of eye-care professionals in reinforcing the importance of modifiable risk factors is vital.

The dietary problem

Canada's Food Guide 2007 recommends seven (7) servings of fruit and vegetables daily for adults >51 years.²⁷ Fruit and vegetables are excellent natural sources of lutein and other antioxidants; however, a large proportion of Canadians >50 years are not consuming the recommended daily allowances (Table 2).²⁸ Antioxidant supplementation may be the answer, as the Rotterdam Eye Study and AREDS studies suggest.^{9, 12, 15, 16}

Consensus

The incidence of AMD is predicted to increase dramatically in coming years due to the aging of Canada's population.

The poor nutritional habits of older Canadians may compound the predicted increase of AMD due to aging.

A large proportion of Canadians are not ingesting the recommended daily allowance of fruit and vegetables.

Age may affect the absorption of nutrients.

Recommendations

Based on current knowledge:

- Physicians and eyecare professionals should educate

adults ≥ 55 years about the risk factors for AMD.

- Physicians and eyecare professionals should forward risk-factor management strategies for the prevention of AMD to patients at risk.
- Physicians and eyecare professionals should counsel patients to stop smoking, minimize sunlight exposure, and maintain a healthy diet.
- The Rotterdam Eye Study suggests that regular dietary intake of specific antioxidant vitamins and minerals may benefit patients at risk of early AMD and those with a family history of AMD. When diet is unable to meet daily vitamin and mineral requirements that may reduce the risk of AMD progression, supplementation is an option for patients at risk. Physicians and eyecare professionals should ascertain patients' normal intake of supplements before recommending further supplements for AMD.
- More research is necessary to examine the benefits, risks, and optimal dosages of vitamin and mineral supplements in patients at risk of AMD.

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Age (Years)	Percentage(%) with AMD	Canadians with AMD*
43 – 53	8.5	467,500
55 – 64	14.4	529,126
65 – 74	19.4	440,768
≥75	36.8	748,512
Estimated total		2,185,906

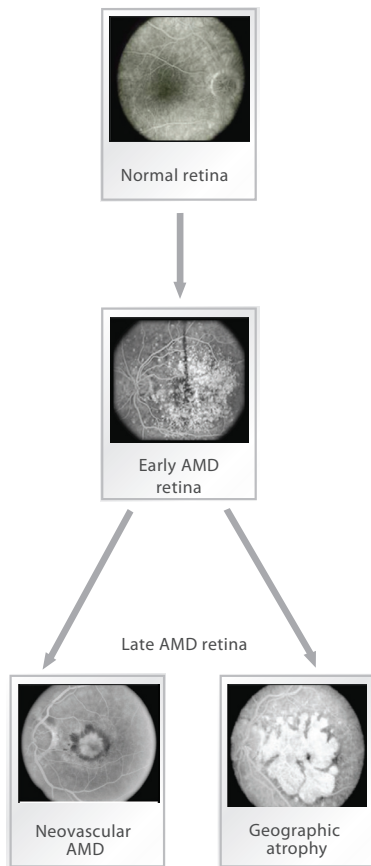
Age (Years)	Percentage(%)
45 – 54	56.8
55 – 64	52.3
65 – 74	48.5
≥75	39.4

* Extrapolated from Beaver Dam Eye Study 1988-1990³
 Population statistics for age groups <65: Statistics Canada 2006 Census;
 For age groups >65, Statistics Canada projections (medium growth), 2005

Statistics Canada. Table 105-0449²⁸

Pathogenesis of AMD

Flourescein Angiograms



CNV = Choroidal neovascularization

Oxidative Stress

