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The Role of Nutritional Supplements in the Management of Age-related Macular Degeneration

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Age-related macular degeneration (AMD) represents a significant risk of worsening vision and blindness as our population ages. The advent of vascular endothelial growth factor (VEGF) inhibitors represents a new standard for the management of patients with neovascular ("wet") AMD; however, few treatment options exist for the atrophic ("dry") form. Supplementation with antioxidant vitamins and minerals, as per the formulation of the Age-Related Eye Disease Study (AREDS), has been shown to reduce the risk of development and progression of AMD. This issue of *Ophthalmology Scientific Update* presents the study data supporting the use of AREDS supplementation, addresses the controversy of the impact of genetics on the effectiveness of supplements, and reviews recommendations for their place in the management of the wet and dry forms of AMD.

As its name implies, age-related macular degeneration (AMD) describes progressive damage to the macula that results in significant vision loss, predominantly in patients aged ≥55-60 years. AMD also develops more frequently in white patients and in women.[1] It is the principal cause of vision loss in Canada.[2,3]

Although the specific mechanisms of AMD pathogenesis have not been elucidated, our awareness of the complex interaction of genetic, inflammatory, oxidative, and immunological processes in both its atrophic ("dry") and neovascular ("wet") forms continues to grow.[4-7] The central player in both forms of AMD is the retinal pigment epithelium (RPE), which, along with the Brüch membrane (BM), separates the photoreceptor cells in the macula from the choroidal blood supply. As drusen accumulate in the space between the RPE and BM, neovascular tissue proliferates into the subretinal space. This leads to degeneration of the RPE and BM (dry AMD) or subretinal neovascularization (wet AMD).

Oxidative stress is another important contributor to the progression of AMD. In the midst of a highly oxidative environment, the retina is particularly susceptible to oxidative damage due to several factors, including light exposure, high concentration of readily oxidizable polyunsaturated fatty acids (PUFAs), and significant oxygen consumption.[8-10] The promotion of free radicals and the naturally occurring accumulation of lipofuscin as we age contribute to oxidative damage in the retina, and the subsequent inflammation contributes to the formation and progression of AMD.[7,11,12] Naturally apparent antioxidant and repair systems counter the oxidative damage; however, the efficiency of these systems diminishes with age.

Rationale for Nutritional Supplements in the Management of AMD

In general, nutritional supplements help to replenish PUFAs such as Ω–3 and other nutrients (eg, zinc) that act against oxidative damage. Research beginning in the early 1960s established the impact of trace elements in retinal disease.[13-15] Based on this research, Newsome et al[16] found that oral zinc was associated with significantly smaller reductions in visual acuity (VA) versus placebo up to 24 months in AMD patients with VA in 1 eye of ≥20/80. Subsequent trials evaluated the potential benefits of zinc and other antioxidants such as vitamins B, C, E, and D, carotenoids (ie, lutein, zeaxanthin, and ß-carotene), and Ω–3, alone or in combination, in slowing the progression of AMD. The pivotal trial in this accumulated body of research was the Age-Related Eye Disease Study (AREDS), sponsored by the National Eye Institute.[17] In this multicentre, prospective study, 3640 patients aged 55-80 years with drusen, noncentral geographic atrophy (GA) or pigment abnormalities in 1 or both eyes, or advanced AMD / vision loss due to AMD in 1 eye were randomized to 1 of 4 treatment groups:

1. Antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and ß-carotene, 15 mg)
2. Zinc (80 mg) and copper (2 mg)
3. Antioxidants + zinc / copper
4. Placebo

Compared with placebo, all active treatments were associated with statistically significant reductions in the risk for the progression to advanced AMD: antioxidants + zinc, odds ratio (OR) 0.72

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(95% confidence interval [CI] 0.52–0.98); antioxidants alone, OR 0.80 (95% CI 0.59–1.09); and zinc alone, OR 0.75 (95% CI 0.55–1.03). The reductions were even greater in subjects with Category 3–4 AMD (extensive intermediate drusen, large drusen, or noncentral GA in 1 or both eyes or advanced AMD or vision loss due to nonadvanced AMD in 1 eye) who are at the highest risk for progression to advanced AMD. The 5-year probability of a ≥15-letter decrease in VA score was 29% for placebo, 23% for antioxidants + zinc, and 26% and 25% for antioxidants and zinc alone, respectively; the reduction with combination therapy was statistically significant.

AREDS2 investigated whether the *addition* of lutein+zeaxanthin, docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA) or both to the standard AREDS formula, decreased the risk of developing advanced AMD (ie, neovascular AMD or GA) to a greater degree than the original AREDS formulation.[18] The authors also tested the effect of removing ß-carotene and reducing the dose of zinc in an optional second randomization. This multicentre, randomized, double-masked trial enrolled 4203 patients with bilateral large drusen or large drusen in 1 eye and advanced AMD in the other. The median follow-up was 5 years. The 4 treatment groups received the AREDS formulation and 1 of the following:

1. Lutein (10 mg) + zeaxanthin (2 mg)
2. DHA (350 mg) + EPA (650 mg)
3. Lutein+zeaxanthin and DHA+EPA
4. Placebo

None of the active treatment groups conferred a statistically significant reduction in progression to advanced AMD compared with the control group. The Kaplan Meier probabilities of progression to advanced AMD were 31% for placebo, 29% (hazard ratio [HR] 0.90; *P*=0.12) for lutein+zeaxanthin, 31% (HR 0.97; *P*=0.70) for DHA+EPA, and 30% (HR 0.89; *P*=0.10) for the combination.

In the optional second randomization, patients were randomized to the unmodified AREDS formulation, the formulation with 25 mg zinc, the formulation without ß-carotene, or the formulation with both the zinc and ß-carotene modifications. Neither of these variations in the AREDS formulation resulted in a significant change in progression to advanced AMD; the HR for low-dose zinc versus the standard dose was 1.06 (*P*=0.32) and for no ß-carotene versus the standard amount of ß-carotene the HR was 1.07 (*P*=0.31). A higher incidence of lung cancer was detected in patients receiving ß-carotene than in those who did not (2.0% versus 0.9%; nominal *P*=0.04); 91% of participants who developed lung cancer were former smokers.

A 10-year follow-up study involving 3549 individuals from the original AREDS determined that patients with Category 3–4 AMD at baseline who used the AREDS formulation experienced statistically significant reductions in the risk of developing advanced AMD (OR 0.66; 95% CI 0.53–0.83; *P*<0.001) and neovascular AMD alone (OR 0.60; 95% CI 0.47–0.78; *P*<0.001).[19]

Impact of Genotypes on the Effectiveness of Nutritional Supplements

Beginning with early studies into hereditary factors in AMD,[20-24] questions arose regarding the role that genetics played in the development, progression, and management of AMD. The AMD Gene Consortium's genome-wide association study involving more than 17 100 cases of advanced AMD and over 60 000 controls of European and Asian ancestry identified 19 genomic loci, including 7 previously unidentified loci, associated with AMD that reached $P<5x10^{-8}$.[25] Genetic risk score indicated that cases and controls could be readily distinguished in all examined samples. Fritsche et al[26] described 52 independently associated common and rare AMD variants ($P<5x10^{-8}$) distributed across 34 loci.

Specific research has identified complement factor H (*CFH*) and the age-related maculopathy susceptibility 2 (LOC387715/*ARMS2*) gene as consistently having the strongest association with AMD.[27-36] Several investigators have focused their investigation on the effect of the different alleles in *CFH* and *ARMS2*, particularly the transitions of thymine – thymine (TT) to cytosine – cytosine (CC) in *CFH* and guanine – guanine (GG) to TT in *ARMS2*. In the Beaver Dam Study,[37] a population-based cohort study involving periodic examination of 4282 individuals aged 43-86 years without AMD over a 20-year period, subjects were divided – based on the presence of 0, 1-2, or 3-4 risk alleles for *CFH* and *ARMS2* – into low (66%), intermediate (26%), and high (8%) genetic risk for AMD. The rates of development of early (presence of medium-sized drusen typically without vision loss) and advanced AMD, respectively, were 33.0% and 1.4% for low risk, 39.9% and 5.2% for intermediate risk, and 46.5% and 15.3% for high risk. Lechanteur et al[38] found that the age of onset of neovascular AMD was 2.8 years earlier in subjects who are homozygous carriers of *CFH* Y402H (*P*=0.02), 5.2 years earlier for homozygous carriers of LOC387715 A69S/*ARMS2*, and 12.2 years earlier among those carrying 4 risk alleles in both *CFH* and *ARMS2* (*P*<0.001) than in the reference group.

Further scientific analysis probed the potential impact of genotypes – especially single nucleotide polymorphisms (SNPs) in *CFH* and *ARMS2* – on the management of AMD. A retrospective logistic regression analysis in 876 AREDS participants who were classified as high risk for the development of advanced AMD found a statistically significant association between the *CFH* Y402H genotype and response to supplementation with antioxidants + zinc.[36] In individuals with the homozygous nonrisk genotype (TT), a reduction of 68% in the progression to advanced AMD was observed with antioxidants + zinc versus placebo. Of those individuals with the homozygous risk

KEY POINTS

- AREDS
  - The AREDS formulation (vitamin C, vitamin E, ß-carotene, zinc, and copper) was associated with a 25% reduction in the risk of progression to advanced AMD in subjects with Category 3–4 AMD.
  - The risk of severe vision loss was reduced by 19% with the AREDS formulation.
- AREDS2 – patients with intermediate AMD (bilateral large drusen) or late AMD in 1 eye:
  - No additional benefit was obtained by the addition of lutein + zeaxanthin and DHA + EPA to the original AREDS formulation.
  - Neither the removal of ß-carotene nor a reduction in the dose of zinc affected the benefit of treatment.
  - Lutein + zeaxanthin can be considered an appropriate substitution for ß-carotene to avoid the potential increased risk of lung cancer associated with ß-carotene in patients with a history of smoking.

genotype (CC), 44% in the placebo group progressed to advanced AMD, compared with 39% in the antioxidant + zinc group, representing a reduction of only 11% (Table 1). It is important to note that, although the benefit of combined nutritional supplementation on reducing AMD progression relative to placebo varied by genotype, this treatment was not associated with a harmful effect (ie, greater progression than among controls) and the results for all groups trended towards a treatment benefit. More recent studies corroborated that the antioxidant-mineral supplement is more effective for the homozygous low-risk or heterozygous *CFH* Y402H genotype and less effective for the homozygous risk genotype in lowering the risk of progression to advanced AMD.[35,39]

Awh et al conducted studies into whether the presence of specific *CFH* and *ARMS2* genetic polymorphisms predict the response to nutritional supplementation.[40,41] They conducted a pharmacogenetic clinical analysis of the AREDS treatment groups in 995 AREDS participants with category 3 AMD in 1 eye and categories 1-4 AMD in the fellow eye.[40] Forward stepwise Cox regression analysis performed within each treatment group demonstrated that AMD progression was significantly associated with *ARMS2* risk allele status in antioxidant-treated patients (P=3.31x10^{-6}) and with *CFH* risk allele status in zinc-treated patients (P=2.41x10^{-7}); both associations were observed whether the agent was taken as monotherapy or in combination. Progression was also significantly associated with the presence of both *CFH* and *ARMS2* in the control group (P=2.29x10^{-4} for *CFH* and 2.30x10^{-2} for *ARMS2*). Cox proportional hazards regression analyses within treatment groups showed that in patients receiving antioxidants only, the presence of 1 and 2 *ARMS2* risk alleles were associated with RRs of AMD progression of 2.58 (P=5.75x10^{-5}) and 3.96 (P=2.22x10^{-6}), respectively. In those taking zinc only, 1 and 2 *CFH* risk alleles were associated with RRs of 2.18 (P=4.16x10^{-2}) and 4.46 (P=7.52x10^{-5}), respectively. Homozygous risk alleles for both *ARMS2* and *CFH* were significant predictors of progression in patients receiving antioxidants + zinc. Finally, patients with 2 CFH risk alleles were found to have a 43% greater rate of progression over 12 years compared with placebo (74% versus 42%). Based on their findings, the authors recommended pharmacogenomic testing to assist with treatment decisions.

KEY POINTS

- Two main genes are associated with AMD:
  - CFH
  - ARMS2
- High-risk genotype carriers have a higher risk of both early and advanced AMD than carriers of the non-risk genotype.
- Risk: homozygous > heterozygous
- The CFH genotype lowers the effectiveness of the AREDS formulation in reducing the risk of progression of AMD.
  - Patients with a homozygous high-risk genotype experienced the greatest reduction in treatment effectiveness.
  - Nonetheless, AMD progression risk is still reduced with the AREDS formulation versus placebo in all genotypes.

Table 1: Response to nutritional supplementation according to genotype[36]

Gene	Genotype[a]	Progression		Treatment vs placebo, relative (absolute) difference
		Treatment	Placebo	
Antioxidants + zinc				
CFH Y402H	TT	11%	34%	68% (-23%)
	TC	2%	31%	35% (-11%)
	CC	39%	44%	11% (-5%)
ARMS2	GG	15%	16%	6% (-1%)
	TG	24%	45%	47% (-21%)
	TT	43%	5%	14% (-7%)
Zinc				
CFH Y402H	TT	17%	34%	50% (-17%)
	TC	25%	31%	19% (-6%)
	CC	44%	44%	0% (0%)
ARMS2	GG	18%	16%	12% (+2%)
	TG	34%	45%	24% (-11%)
	TT	5%	5%	0% (0%)
Antioxidants				
CFH Y402H	TT	38%	34%	12% (+4%)
	TC	38%	31%	23% (+7%)
	CC	5%	44%	14% (+6%)
ARMS2	GG	23%	16%	44% (+7%)
	TG	47%	45%	4% (+2%)
	TT	59%	0.5%	18% (+9%)

[a] For CFH, T represents the non-risk allele and C represents the risk allele; thus, TT is a homozygous nonrisk type.
NOTE: Nearly every group experienced a reduction in risk with nutritional supplements. Response varied according to genotype.

Awh et al repeated their evaluation of AMD progression in an AREDS cohort (N=989) randomized to 1 of the 4 AREDS treatment groups relative to the presence of *CFH* and *ARMS2* risk alleles over 7 years.[41] The 4 genotype groups (GTGs) were as follows:

- GTG 1: 0-1 *CFH* risk alleles, 0 *ARMS2* risk alleles
- GTG 2: 2 *CFH* risk alleles, 0 *ARMS2* risk alleles
- GTG 3: 0-1 *CFH* risk alleles, 1-2 *ARMS2* risk alleles
- GTG 4: 2 *CFH* risk alleles, 1-2 *ARMS2* risk alleles

Relative to GTG 1, the HRs for AMD progression were 1.87 for GTG 2 (P=2.93x10^{-3}), 2.00 for GTG 3 (P=4.93x10^{-5}), and 3.07 for GTG 4 (P=4.53x10^{-11}). Each GTG was then analyzed relative to the impact of each treatment on progression, using Cox regression HRs. The results, relative to placebo, are shown in Table 2. As shown, only antioxidant treatment was associated with reduced AMD progression in GTG 1, relative to placebo. GTG 2 patients treated with either zinc-containing formulation experienced significant increases in progression. Conversely, GTG 3 patients derived significant benefit from zinc-based therapy in reducing the progression of AMD. None of the treatments produced significant changes in progression among GTG 4 patients.

Other groups, however, demonstrated no significant effect of genotypes on AMD progression in their study populations. Chew et al for the AREDS Research Group[42] conducted a retrospective evalu-

ation, using a Cox proportional hazards model, of the effect of genotypes on progression to late AMD (ie, neovascular AMD or central GA) according to the 4 AREDS treatment groups. The authors constructed a 2x2 factorial design and, in order to render the study as comparable to those of Awh et al as possible, conducted pairwise comparisons to determine the effect of each regimen as a function of each genotype. Within their statistical model, 385 of 1237 AREDS participants developed late AMD. Significant association was identified between progression and the presence of *CFH* (P=0.005) and *ARMS2* (P<0.0001) genotypes: AMD progression was detected in 17.9%, 25.7%, and 38.6% of patients with low-, medium-, and high-risk *CFH* genotypes, respectively, and in 18.5%, 35.9%, and 48.3% for low-, medium-, and high-risk *ARMS2* genotypes, respectively. None of the pairwise assessment of each combination of genotype profile with each treatment option showed a statistically significant interaction, as defined by P<0.001 with the Bonferroni correction. An analysis of alternate genetic variants for CFH and ARMS2, designed to mirror the first Awh study, failed to identify a statistically significant interaction between treatment effect and genotype (P=0.45).

Chew et al[43] subsequently organized an AREDS "residual cohort", comprising 526 patients who were not included in the second analysis of Awh et al, because the deoxyribonucleic acid was not available to them at that time. The AMD progression outcomes of this cohort differed significantly from those of the Awh study, as shown in Figure 1.

Thus, for all 4 of the genotypic groups reported by Awh et al, the combination of antioxidants and zinc was found to be beneficial in the residual cohort. Chew et al concluded that there was an inherent selection bias in the results reported by Awh in 2015; genetic subgroups were not prespecified and subgroup definitions were derived from the same data used to evaluate their effectiveness. In light of the ensuing controversy as to whether genetic testing should be required before initiating nutritional supplements, an in-depth review of the methodologies of the Awh and Chew trials was presented by Wittes and Musch.[44] The authors – a statistician and an epidemiologist – point out limitations in both trials. They concluded that the small sample sizes issued from the 27 comparisons in the paper of Chew et al make the clinical interpretation of the results difficult, but highlighted (in their opinion) more important statistical difficulties in the Awh trial. Specifically, they found that there was inadequate correction for multiple statistical testing and retrospective data fitting. Wittes and Musch also took issue with *post hoc* exploration of subgroups, which they said provides a high probability both of finding between-group differences and that the findings are spurious, and with Awh et al's definition of subgroups by post-randomization variables. They concluded that genotyping should not be mandatory before prescribing AREDS supplementation for the reduction in the risk of progression of AMD.

Table 2: Risk of progression to advanced age-related macular degeneration according to genotype group (GTG)[41]

GTG[a]	HR (95% CI)	*P*	Conclusion
1: Antioxidants only Zinc only Antioxidants+zinc	0.38 (0.16–0.93) 1.03 (0.50–2.14) 0.80 (0.39–1.63)	0.03 0.93 0.54	Antioxidants only reduced AMD
2: Antioxidants only Zinc only Antioxidants+zinc	1.33 (0.48–3.96) 3.07 (1.18–8.00) 2.73 (1.04–7.20)	0.61 0.02 0.04	Zinc increased progression
3: Antioxidants only Zinc only Antioxidants+zinc	0.72 (0.44–1.18) 0.51 (0.31–0.86) 0.57 (0.35–0.93)	0.19 0.01 0.03	Zinc reduced progression
4: Antioxidants only Zinc only Antioxidants+zinc	0.85 (0.49–1.48) 0.93 (0.53–1.65) 0.88 (0.50–1.55)	0.56 0.82 0.65	None of the treatment options reduced progression

[a] GTG 1 = 0-1 *CFH*, 0 *ARMS2*; 2 = 2 *CFH*, 0 *ARMS2*; 3 = 0-1 *CFH*, 1-2 *ARMS2*; 4 = 2 *CFH*, 1-2 *ARMS2*
HR = hazard risk; CI = confidence interval
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KEY POINTS

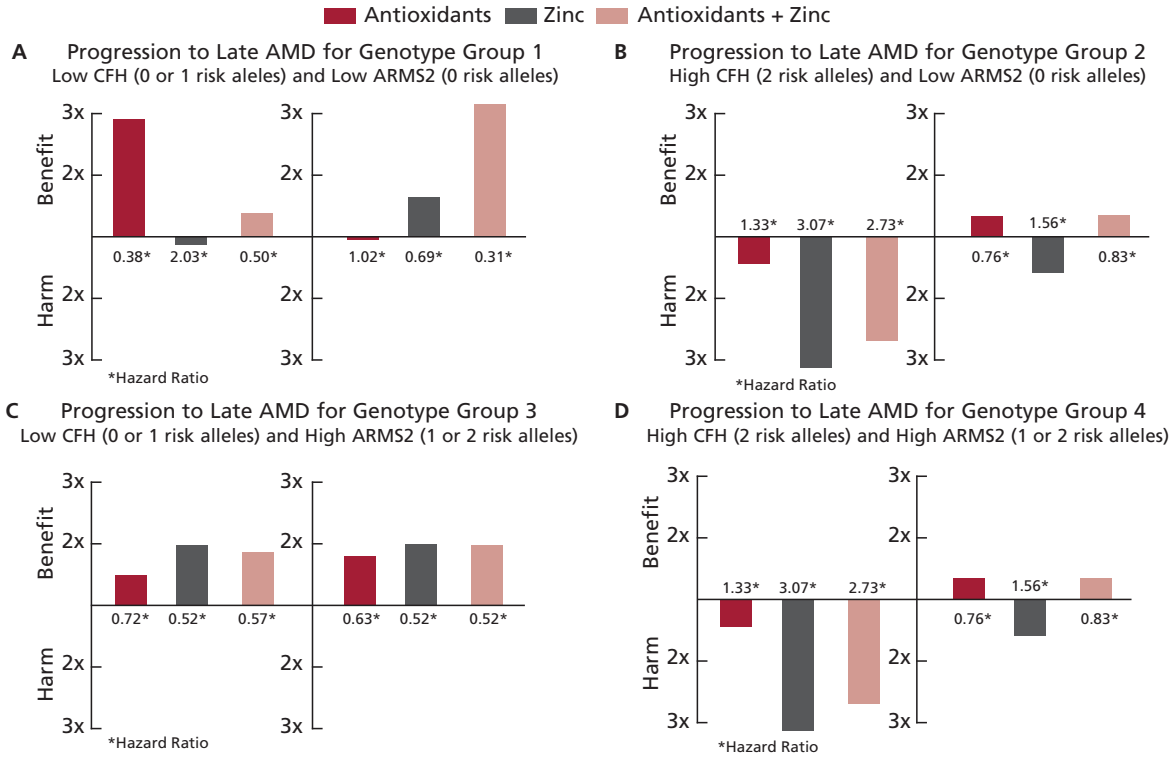
- There is controversy surrounding clinical study of the effects of genotypes on the benefit of the AREDS formulation.
  - Awh et al studies:[40,41]
    - 2 CFH alleles with no ARMS2 alleles showed progression of AMD with zinc-containing therapy.
    - 0-1 CFH alleles with 1-2 ARMS2 alleles showed benefit in reducing AMD progression with zinc-containing therapy.
  - Chew et al studies:[42,43]
    - Neither homogeneous nor heterogeneous genotypes had an effect on AREDS treatment.
  - Wittes and Musch:[44]
    - Genetic subgroups in the report by Awh et are both post hoc and improper. The approach that Awh et al used in defining their genotype subgroups is circular; after selecting post-randomization outcomes observed by Awh et al to define subgroups in the study by Awh et al, they then tested those subgroups with the very same data.

In their 2014 recommendations, the American Academy of Ophthalmology (AAO) Task Force on Genetic Testing[45] maintained their reservation about the benefit of genetic testing in patients with AMD: "Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published prospective clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies."

Nutritional Supplements in Current Clinical Practice

Patients with early signs of dry AMD should be monitored by an ophthalmologist or optometrist at least every 12 months and counselled on lifestyle changes and awareness of signs and symptoms of development of wet AMD.[46] The Canadian

Figure 1: Hazard ratios for AREDS treatment groups according to genotype: comparison of results from Awh et al[41] with Chew et al[43]



Ophthalmological Society and Canadian Association of Optometrists recommend the daily use of AREDS supplementation in patients with moderate to severe dry AMD.[2,46] This position is also supported by the AAO.[47]

The established first-line therapy for patients with wet AMD has become intravitreal anti-VEGF agents.[2,46,47] The AAO advocate early use of the AREDS supplementation towards the reduction of risk of AMD progression.[47]

Conclusion

Ongoing research adds to the picture of AMD as a highly complex disease with both heritable and environmental risks. Although anti-VEGF agents have revolutionized the management of the more serious wet form of AMD, few treatment options are available for its dry counterpart. Antioxidant vitamin and mineral supplementation, according to the AREDS formulation, has been shown to reduce the risk of development and progression of AMD. Controversy persists regarding the potential genetic role in affecting the value of supplementation. In the absence of large-scale, prospective trial evidence, the AREDS formulation remains a safe and effective management option in AMD patients.

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