

SCIENCE IN FOCUS

PreserVision AREDS3™ and the Case for B Vitamins in AMD

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KEY TAKEAWAYS

- Suboptimal B-vitamin status can contribute to accumulation of homocysteine, a metabolic byproduct associated with endothelial dysfunction, oxidative stress, cellular injury and AMD incidence and progression.
- Scientific evidence links elevated homocysteine and suboptimal B-vitamin status with AMD: higher homocysteine has been reported in patients with advanced AMD, and vitamin B12 deficiency has been associated with incident AMD.
- In a prospective randomized study, combined folic acid (vitamin B9) and vitamins B6 and B12 reduced confirmed AMD by 34% and visually significant AMD by 41% versus placebo over a mean 7.3 years.
- Long-term cohort data, AREDS and AREDS2 dietary analyses, and experimental studies provide converging support for B-vitamin-dependent pathways as a biologically plausible extension of AMD nutritional care.

PreserVision AREDS3™ and the Rationale for Adding B Vitamins

Nutritional intervention in AMD rests on a solid evidence base. The AREDS study, published in 2001, showed that high-dose antioxidants plus zinc reduced the odds of progression to advanced AMD (OR 0.72; 99% CI 0.52–0.98). AREDS2, published in 2013, refined that formulation. However, substantial risk remains, including incident AMD and progression to advanced disease^{1,2}.

This Science in Focus article reviews the rationale for PreserVision AREDS3™, an over-the-counter supplement designed to build on the established AREDS2 formulation by adding a B-vitamin complex. It examines why B vitamins have attracted interest in AMD and the potential underlying mechanisms. A companion Science in Focus article will return to the fundamentals of AREDS and AREDS2, analyze the clinical findings, and consider how PreserVision AREDS3™ may be embedded into clinical practice.

Looking Beyond the Retina in Early AMD

Early AMD presents a clinical paradox. Drusen and pigmentary changes are visible on examination, yet vision is often preserved and patients may not experience symptoms. This stage is of considerable scientific and clinical interest, as it offers an opportunity to investigate potentially modifiable pathways that may be active before substantial retinal damage and vision loss make the disease apparent.

AMD is multifactorial. Age, genetic susceptibility and smoking remain the most consistently identified contributors. In addition, the pathophysiology of the disease reflects oxidative stress at the photoreceptor–retinal pigment epithelium interface, chronic low-grade inflammation and choroidal perfusion. Notably, the outer retina has high metabolic demands and relies on an intact choroidal blood supply, making systemic metabolic and vascular health relevant areas of investigation.

While AREDS and AREDS2 established the role of antioxidant and mineral supplementation in reducing progression risk to advanced disease stages, they were not powered to inform incidence or early progression. That evidence gap has encouraged interest in complementary pathways, including B-vitamin-dependent pathways, that may connect systemic metabolic health with retinal vulnerability.

Why Homocysteine Has Attracted Attention

Homocysteine is a byproduct of the metabolism of the essential amino acid methionine. Under physiological conditions, homocysteine is metabolized and cleared via two vitamin-dependent pathways: it can be remethylated back to methionine, a process requiring folate (vitamin B9) and vitamin B12, or it can be irreversibly converted through the transsulfuration pathway toward cysteine, a process requiring vitamin B6 (Reviewed in ³).

If production is excessive, or clearance is insufficient, homocysteine can accumulate. Elevated homocysteine levels have been associated with cardiovascular and cerebrovascular disease, renal disease and dementia. Mechanistically, hyperhomocysteinemia has been linked with endothelial dysfunction, oxidative stress, altered clotting and cellular injury. These systemic associations are important for AMD because the outer retina and choroid may be vulnerable to similar processes⁴.

In an ancillary study of 934 AREDS participants, plasma homocysteine was higher in participants with advanced AMD than in those with no AMD (9.51 versus 8.81 $\mu\text{mol/L}$; $P = .01$), and homocysteine levels above 12 $\mu\text{mol/L}$ were associated with higher odds of AMD after adjustment for age, sex, smoking, cardiovascular history and other covariates. The authors concluded that the findings were consistent with a possible association and that homocysteine may constitute a modifiable risk factor for AMD⁵.

The Role of B Vitamins in Homocysteine Metabolism

Folate (vitamin B9), vitamin B12 and vitamin B6 are key cofactors in the metabolic pathways that clear homocysteine and help keep circulating levels within a physiological range. It is well established that lower folate, vitamin B12 or vitamin B6 status can contribute to higher circulating homocysteine, while B-vitamin repletion or supplementation can lower it⁴.

Clinical observations support that association in AMD. A systematic review and meta-analysis found higher plasma homocysteine in AMD cases than in controls, alongside lower vitamin B12 levels in AMD cases⁶. These findings place homocysteine metabolism within a clinically relevant disease pathway for AMD and pose the question of whether B-vitamin supplementation could have an impact on incidence and progression of AMD beyond the combination tested in AREDS2.

From Biological Rationale to Clinical Evidence

Four complementary lines of evidence address that question. Across randomized, prospective observational, dietary and experimental research, the direction of evidence supports B-vitamin metabolism as a credible and potentially actionable pathway in AMD.

Randomized evidence: incident AMD. The Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) randomized 5,442 female health professionals aged 40 years or older with cardiovascular disease or at least three cardiovascular risk factors to a daily combination of folic acid (B9) 2.5 mg, pyridoxine hydrochloride (B6) 50 mg and cyanocobalamin (B12) 1 mg, or to placebo. The ocular analysis included the 5,205 participants without an AMD diagnosis at baseline. Over a mean 7.3 years of treatment and follow-up, women randomized to combined folic acid and vitamins B6 and B12 experienced fewer medically confirmed cases of AMD than those receiving placebo: 55 versus 82 cases (relative risk [RR] 0.66; 95% CI 0.47–0.93; $P = .02$). For visually significant AMD, there were 26 versus 44 cases (RR 0.59; 95% CI 0.36–0.95; $P = .03$).⁷

Observational evidence: homocysteine and B-vitamin status. The Blue Mountains Eye Study followed 1,760 participants over 10 years. Each 1-standard-deviation rise in serum total homocysteine was associated with incident early AMD (OR 1.33; 95% CI 1.09–1.63), and vitamin B12 deficiency was associated with both incident early AMD (OR 1.58; 95% CI 1.06–2.36) and incident late AMD (OR 2.56; 95% CI 1.38–4.73). These prospective findings extend the WAFACS signal across the disease continuum and identify homocysteine and B-vitamin status as clinically relevant variables.⁸

Dietary evidence: progression to late AMD. In an analysis of 14,135 eyes from AREDS and AREDS2 participants followed for a median of 10.2 years, vitamin B6 and folate were among nine nutrients whose higher intake was significantly associated with a lower risk of progression to late AMD ($P \leq 0.0005$). Although based on reported dietary intake rather than a supplementation intervention, the scale, duration and strong statistical signal directly connect B-vitamin exposure with the outcome that AREDS-based nutritional strategies are designed to influence.⁹

Experimental evidence: biological plausibility. Experimental models show that hyperhomocysteinemia can disrupt RPE structure and function and compromise blood–retinal barrier integrity through oxidative stress, endothelial dysfunction, inflammation and impaired cellular methylation. These mechanisms provide a biologically coherent explanation for the clinical and epidemiological findings and connect systemic metabolic health with retinal vulnerability¹⁰.

Taken together, these independent lines of evidence reinforce one another: randomized data show fewer AMD events with combined B vitamins; long-term cohorts link homocysteine and B-vitamin status with incident disease; AREDS and AREDS2 dietary analyses associate B6 and folate with lower progression risk; and experimental studies demonstrate credible retinal pathophysiological mechanisms.

Beyond Homocysteine: Broader Roles for B Vitamins

The evidence reviewed above positions homocysteine as a coherent link between systemic metabolism, B-vitamin status and AMD biology. Importantly, this does not limit the rationale for B vitamins to homocysteine alone.

Beyond B6, B9 and B12, the literature points to additional pathways that may be relevant to retinal resilience. A recent review by Poteet et al. highlights B vitamins involved in mitochondrial function, including B1, B2, B3, B5, B7, B9 and B12; experimental work describing RPE-related effects for B2 and B3/nicotinamide; and clinical evidence that B3/niacin can influence choroidal blood volume in patients

with AMD. These examples support a conclusion in which homocysteine lowering remains relevant, but not exclusive, to the rationale for B-vitamin support (Reviewed in ^{3,11}).

Broadening the Nutritional Perspective in AMD

Nutritional intervention in AMD rests on a solid evidence base. The next opportunity is to build on that foundation by addressing additional, complementary pathways implicated across the AMD continuum. There is a consistent rationale suggesting that adding a B-vitamin complex to the already established AREDS2 formulation could extend nutritional support in AMD patients. B vitamins have been linked to several biological processes relevant to ocular health, and homocysteine metabolism provides one plausible mechanistic link.

In this article we have reviewed the clinical literature supporting this hypothesis. In this context, WAFACS is especially important because it provides randomized evidence over more than seven years and demonstrates clinically meaningful relative reductions of 34% in confirmed AMD and 41% in visually significant AMD. The ocular analysis was ancillary and involved women with elevated cardiovascular risk, but medical-record confirmation, long follow-up and consistent effects across both AMD endpoints make the findings a compelling proof of concept for the addition of B vitamins⁷.

The available evidence is sufficiently relevant to support further development of this combined nutritional strategy. Future prospective studies can refine patient selection, disease stage and biomarker use, and quantify effects using modern retinal imaging and vision endpoints. In the meantime, the existing evidence provides a strong scientific rationale for PreserVision AREDS3™ as a next-generation approach to AMD nutritional care. Readers may also wish to consult the companion Science in Focus article on AREDS and AREDS2 clinical evidence, as well as the Poteet and Johnson reviews available in this website.

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Author Disclosures

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Availability Statement

PreserVision AREDS3™ is available in the US. However, it is not available worldwide. Contact us for further information about PreserVision AREDS3™ availability.