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COMMENTARY

# Role of B Vitamins in Preventing the Development and Progression of Age-Related Macular Degeneration

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## ABSTRACT

No current treatments are curative for age-related macular degeneration (AMD), and preventing disease progression is challenging. Dietary factors play a role in the course of macular degeneration, and management of AMD commonly includes nutraceuticals (e.g., supplementation with a combination of antioxidant vitamins and minerals). This commentary summarizes the existing literature, emerging evidence, and upcoming research on the role of B vitamins in both preventing the development of AMD and slowing its progression.

**Keywords:** Age-related macular degeneration; B vitamins; Nutritional supplements

**Key Summary Points**

Age-related macular degeneration (AMD) is a leading cause of vision loss in older adults, and while there is no cure, nutritional interventions can help slow progression.

Two studies, the Age-Related Eye Disease Study (AREDS) and AREDS2, demonstrated that specific combinations of antioxidant vitamins and minerals—particularly those including lutein and zeaxanthin—reduce the risk of progression to late-stage AMD.

Emerging evidence highlights the potential role of B vitamins (especially $B_6$, $B_9$, and $B_{12}$) in both reducing the risk of AMD development and slowing its progression.

Low levels of B vitamins may be associated with higher AMD risk, possibly due to increased homocysteine levels that damage retinal tissue through oxidative stress and inflammation.

The upcoming AREDS3 trial will assess whether adding higher-dose B vitamins to current supplements can provide additional protective benefits, especially for early-stage AMD.

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## INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of blindness and visual impairment throughout the world [1, 2]. Intermediate-stage AMD, which may be asymptomatic, can progress to either atrophic (dry) AMD or neovascular (wet or exudative) AMD [1]. Preventing AMD progression is challenging, as the pathogenesis is incompletely understood. Processes implicated in AMD include an interconnected network of increased oxidative stress, mitochondrial dysfunction, and inflammatory activation [3]. There are currently no treatments that are curative for AMD; rather, the focus of available therapies is on the prevention or slowing of disease progression [2].

Intake of specific nutrients and antioxidant supplements has been shown to reduce the risk of progression from intermediate to late/advanced AMD [2]. For example, data from the Age-Related Eye Disease Study (AREDS) randomized, placebo-controlled clinical trial demonstrated that supplementation with a combination of antioxidant vitamins and minerals (vitamin C, vitamin E, β-carotene, zinc, and copper; Table 1) [4] reduced the risk of progressing from intermediate to advanced AMD by 25% over 5 years [5]. In a subsequent randomized, placebo-controlled study, AREDS2, patients who were assigned to treatment with a modified version of the original AREDS supplement (addition of lutein and zeaxanthin; removal of β-carotene) had an 18% lower risk of progression to late AMD and a 22% lower risk of neovascular AMD compared with those who received the original AREDS supplement [6]. The proposed mechanisms for macular protection of carotenoids in AREDS2 includes neutralization of free radicals, thereby reducing oxidative stress and inflammation, and protection from blue light-mediated damage by increasing the macular pigment (Fig. 1) [7].

A supplement with an updated nutrient formula that includes the B vitamin complex, $B_1$, $B_2$, $B_3$, $B_5$, $B_6$, $B_7$, $B_9$, and $B_{12}$, is in development with the National Eye Institute for testing in the AREDS3 clinical trial. This brief review will describe the available data supporting the use of B vitamins to reduce the risk of AMD development and progression. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Table 1** Commercially available formulas based on AREDS/AREDS2 [4]

| Nutrient | AREDS formula[a] | AREDS2 formula |
|---|---|---|
| Vitamin C | 500 mg | 500 mg |
| Vitamin E | 400 IU | 400 IU |
| Beta-carotene | 15 mg | – |
| Copper (cupric oxide)[b] | 2 mg | 2 mg |
| Lutein | – | 10 mg |
| Zeaxanthin | – | 2 mg |
| Zinc | 80 mg | 80 mg |

*AREDS* Age-Related Eye Disease Study, *IU* international units

[a]Not recommended for current or former smokers

[b]Added to avoid zinc-related copper deficiency

## ROLE OF DIETARY INTAKE OF B VITAMINS IN AMD DEVELOPMENT AND PROGRESSION

Accumulated clinical evidence supports a role for B vitamins in preventing the development of AMD and slowing AMD progression (Table 2) [5, 8–20]. Most data linking B vitamins and AMD are derived from observational studies that quantified dietary consumption or serum concentrations and compared these values in patients who had AMD at baseline or developed AMD during follow-up versus patients without AMD.

### Development of AMD

In a 2015 meta-analysis of 11 case–control studies, patients with AMD had lower average plasma

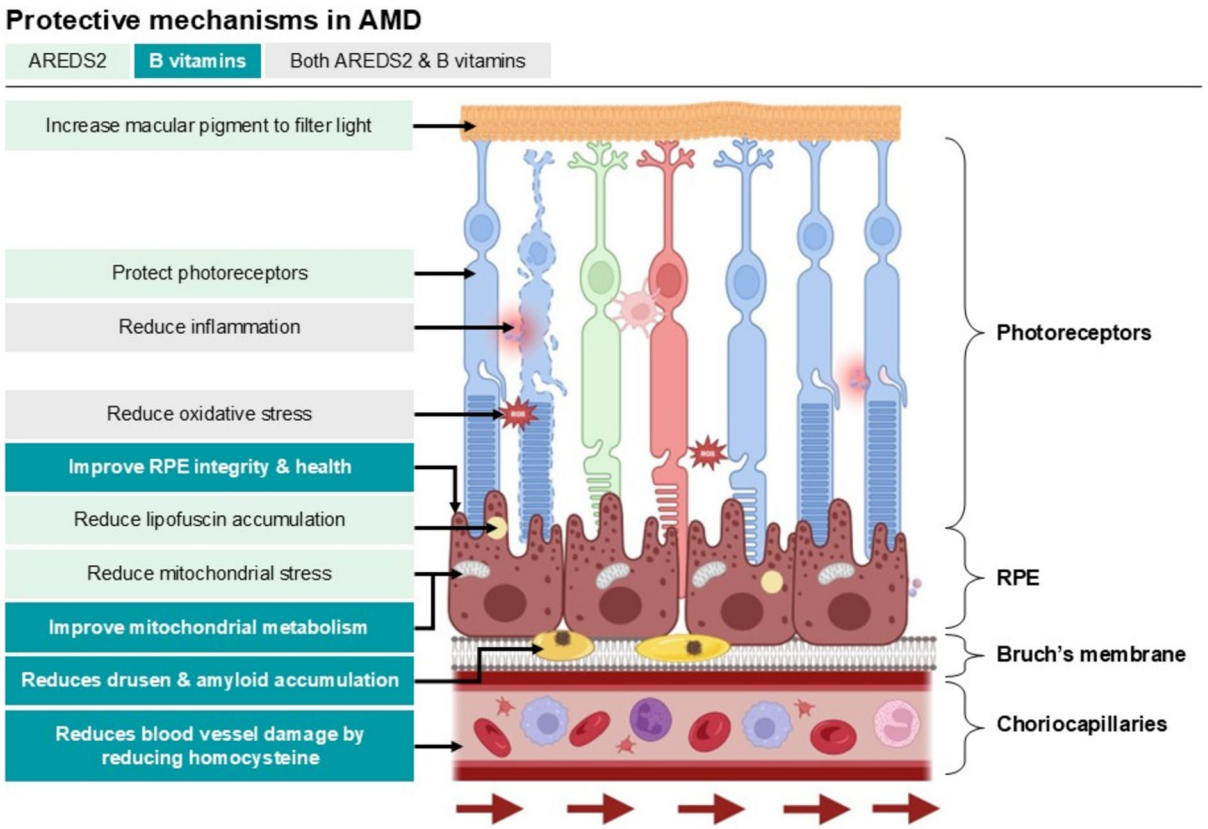


**Fig. 1** Hypothesized vitamin B protective mechanisms in AMD [7, 33, 35, 37–39, 42]. Schematic representation of the structural and cellular organization of retina with underlying RPE in early AMD. *AMD* age-related macular degeneration, *AREDS2* Age Related Eye Disease Study 2, *RPE* retinal pigment epithelium

vitamin $B_{12}$ concentrations compared with the control group [8]. In the overall population, no differences were observed in serum vitamin $B_9$ concentrations in patients with AMD versus the control group; however, for patients with neovascular AMD, average serum vitamin $B_9$ concentrations were lower than in patients with any AMD [8].

In the population-based Blue Mountains Eye Study-2 (BMES-2), risk of developing AMD increased more than twofold with low serum vitamin $B_{12}$ concentration (< 125 pmol/L) (odds ratio [OR] 2.30 [95% confidence interval (CI) 1.08–4.89]) and by more than threefold for patients with low serum vitamin $B_{12}$ who did not have elevated serum total homocysteine (≤ 15 µmol/L; OR 3.74 [95% CI 1.06–13.24]), suggesting vitamin $B_{12}$ levels may influence AMD risk via mechanisms other than homocysteine metabolism [12]. An analysis of data from BMES-2 through BMES-4 assessed incident early, late, and any AMD separately [13]. Vitamin B-related risk factors for early AMD and for any AMD included vitamin $B_{12}$ deficiency (< 185 pmol/L) and vitamin $B_9$ deficiency (< 11 nmol/L). Risk for late AMD increased with vitamin $B_{12}$ deficiency [13]. Conversely, greater serum vitamin $B_{12}$ concentration decreased the risk for incident early, late, and any AMD [13]. Moreover, vitamin $B_{12}$ supplementation decreased the risk for incident early AMD by 42% (OR 0.58 [95% CI 0.35–0.98]) and the risk of any AMD by 47% (OR 0.53 [95% CI 0.33–0.85]) [13].

The Alienor Study, a prospective, population-based cohort study that evaluated adults aged ≥ 73 years at baseline, reported that the risk for advanced AMD decreased by 51%

**Table 2** Associations between vitamin B and/or homocysteine concentrations and development or progression of AMD

| Study | Study design | Population | Vitamin B findings | Homocysteine findings |
|---|---|---|---|---|
| Meta-analysis[a] (Huang 2015) [8] | Meta-analysis of case–control studies ($N = 11$) | Patients with AMD ($n = 1072$) and non-AMD controls ($n = 1202$) | ↓ Plasma $B_{12}$ in AMD vs. controls[b]<br>↓ Serum $B_9$ in neovascular AMD vs. any AMD[b] | ↑ Serum tHcy in AMD vs. controls<br>↑ Serum tHcy in neovascular AMD vs. any AMD |
| Meta-analysis (Pinna 2018) [20] | Meta-analysis of case–control studies ($N = 10$) | Patients with neovascular AMD ($n = 453$) and non-AMD controls ($n = 514$) | Not assessed | ↑ serum tHcy in neovascular AMD vs. controls |
| AREDS (Merle 2016) [9] | Prospective cohort study | Patients aged 55–80 years with drusen, noncentral GA, or pigment abnormalities in 1 or both eyes; or advanced AMD or vision loss due to AMD in 1 eye [5] | Risk of progression to GA decreased with ↑ dietary intake of $B_9$<br>No significant association with progression to GA observed for $B_1$, $B_2$, $B_3$, $B_6$, or $B_{12}$<br>No B vitamins were associated with progression to neovascular AMD | Not assessed |

**Table 2** continued

| Study | Study design | Population | Vitamin B findings | Homocysteine findings |
|---|---|---|---|---|
| AREDS 1 and AREDS 2 (Agrón 2021) [10] | Post hoc analysis of 2 controlled clinical trial cohorts | Participants in AREDS 1 (no AMD to unilateral late AMD) and AREDS 2 (bilateral large drusen or unilateral late AMD)<br>This analysis included eyes with no late AMD at baseline (14,135 eligible eyes; 8130 participants) | Risk of progression to late AMD decreased with ↑ dietary intake of $B_6$ and $B_9$ (nominal for $B_1$, $B_3$)<br>Risk of progression to GA decreased with ↑ dietary intake of $B_9$ (nominal for $B_1$, $B_2$, $B_3$, $B_6$, $B_{12}$)<br>Risk of progression to neovascular AMD nominally decreased with ↑ dietary intake of $B_6$<br>Risk of progression to large drusen nominally decreased with ↑ dietary intake of $B_9$[c] | Not assessed |
| Alienor Study (Merle 2022) [11] | Prospective, population-based cohort | Residents of Bordeaux, France, aged ≥ 73 years at baseline ($N = 861$) | Risk for advanced AMD decreased with<br>• Serum $B_9$ ≥ 10 nmol/L (normal vs. deficient)<br>• ↑ Dietary intake of $B_5$ and $B_6$<br>No significant association was observed between incidence of advanced AMD and dietary intake of $B_1$, $B_2$, $B_3$, $B_9$, and $B_{12}$ or serum $B_6$ and $B_{12}$ | Not assessed |

**Table 2** continued

| Study | Study design | Population | Vitamin B findings | Homocysteine findings |
|---|---|---|---|---|
| Blue Mountains Eye Study 2 (BMES-2) (Rochtchina 2007) [12] | Population-based, cross-sectional analysis | Noninstitutionalized residents of Sydney, Australia, aged > 49 years ($N = 2335$) | Risk for AMD increased with<br>• Low serum $B_{12}$ (< 125 pmol/L)<br>• Low serum $B_{12}$ in patients with tHcy > 15 μmol/L<br>No significant association was observed for $B_9$ | Serum tHcy > 15 μmol/L increased risk of AMD in patients aged < 75 years<br>↑ Serum tHcy nonsignificantly increased risk of AMD in overall population |
| Blue Mountains Eye Study (BMES-2 to BMES-4) (Gopinath 2013) [13] | Population-based cohort study | Noninstitutionalized residents of Sydney, Australia, aged ≥ 49 years ($N = 1390$) | Risk for incident early AMD increased with<br>• $B_{12}$ deficiency (< 185 pmol/L)<br>• $B_9$ deficiency (< 11 nmol/L)<br>Risk for incident late AMD increased with<br>• $B_{12}$ deficiency<br>Risk for incident any AMD increased with<br>• $B_{12}$ deficiency<br>• $B_9$ deficiency<br>↑ Serum $B_{12}$ decreased risk of incident early and any AMD<br>Risk for incident early and any AMD decreased with supplementary vitamin $B_{12}$ intake | ↑ Serum tHcy increased risk of incident early and any AMD |
| Case–control study (Gopinath 2017) [14] | Case–control study | Patients aged ≥ 60 years with late AMD ($n = 480$) and age- and sex-matched controls without AMD ($n = 518$)<br>Comparator group was from BMES-3 and BMES-4 | ↓ Dietary intake of $B_9$ in patients with late AMD vs. controls | Not assessed |

**Table 2** continued

| Study | Study design | Population | Vitamin B findings | Homocysteine findings |
|---|---|---|---|---|
| Case–control study (Šalková Kráľová 2023) [15] | Case–control study | Patients with AMD ($n = 93$) and non-AMD controls ($n = 58$) from a single clinic in the Czech Republic | ↓ Dietary intake of $B_2$, $B_3$, $B_5$, $B_6$ in AMD vs. controls<br>No significant difference between AMD and controls for dietary intake of $B_1$, $B_9$, $B_{12}$ | Not assessed |
| Coimbra Eye Study (Nunes 2018) [16] | Case–control study (nested in a cross-sectional, population-based study) | Patients aged > 55 years with AMD ($n = 768$) and age- and sex-matched controls without AMD ($n = 1224$) | ↓ Dietary intake of $B_9$ in patients with AMD | Not assessed |
| NHANES (Heuberger 2002) [17] | Cross-sectional observational study | A nationally representative sample of the civilian noninstitutionalized US population (from the NHANES 1988–1994) aged ≥ 40 years ($N = 3527$) | No association was observed between red blood cell $B_9$ or serum $B_{12}$ and ARM<br>↓ Red blood cell $B_9$ was associated with soft drusen in non-Hispanic Black patients | No association was observed between serum tHcy and early or late ARM |
| NHANES (Zheng 2023) [18] | Cross-sectional observational study | Participants in the NHANES 2005–2008 aged ≥ 40 years ($N = 5107$)<br>Patients with late AMD ($n = 53$); patients without AMD ($n = 5054$) | Risk for late AMD decreased with ↑ dietary intake of $B_1$<br>No significant association was observed between early AMD and dietary intake of $B_1$ | Not assessed |

**Table 2** continued

| Study | Study design | Population | Vitamin B findings | Homocysteine findings |
|---|---|---|---|---|
| NHANES (Liu 2024) [19] | Cross-sectional observational study | Participants in the NHANES 2005–2008 aged ≥ 40 years ($N = 1627$)<br>Patients with AMD ($n = 70$); patients without AMD ($n = 1557$) | ↓ Dietary intake of $B_1$, $B_2$, $B_6$, $B_9$, and $B_{12}$ in AMD vs. controls<br>Associations between $B_1$, $B_2$, and $B_6$ and AMD were influenced by the presence of diabetes<br>Association between $B_9$ and AMD was influenced by BMI<br>Causal relationship between $B_{12}$ and AMD was observed for men but not women | Not assessed |

*AMD* age-related macular degeneration, *AREDS* Age-Related Eye Disease Study, *ARM* age-related maculopathy, *BMI* body mass index, *GA* geographic atrophy, *NHANES* National Health and Nutrition Examination Survey, *tHcy* total homocysteine

[a]Studies that were included in this meta-analysis were not included separately in this table

[b]Data are from 3 studies

[c]For progression to large drusen, the cohort included 5399 eligible eyes, 3164 participants

(hazard ratio [HR] 0.49 [95% CI 0.25–0.95]; $P=0.036$) at normal concentrations of serum vitamin $B_9$ (≥ 10 nmol/L) and by up to 28% (HR 0.72 [95% CI 0.53–0.99]; $P=0.049$) and 10% (HR 0.90 [95% CI 0.81–0.99]; $P=0.049$) with greater dietary intake of vitamins $B_5$ and $B_6$, respectively [11]. An earlier case–control study assessed dietary intake of micronutrients and food groups in patients aged ≥ 60 years with late-stage AMD compared with age- and sex-matched non-AMD controls [14]. The investigators reported significantly lower dietary intake of vitamin $B_9$ in patients with late AMD versus controls ($P<0.0001$) [14]. Notably, data were not reported for other B vitamins. Significantly lower dietary intake of vitamin $B_9$ in patients with AMD compared with age- and sex-matched controls ($P<0.05$) was also reported in the Coimbra Eye Study, a case–control study that included patients aged > 55 years [16].

Several studies evaluated dietary intake of B vitamins and risk of AMD in a nationally representative sample of US adults aged ≥ 40 years using data from the National Health and Nutrition Examination Survey (NHANES) [17–19]. Analysis of data from NHANES 2005–2008 demonstrated that patients with AMD had a significantly lower dietary intake of vitamins $B_1$, $B_2$, $B_6$, $B_9$, and $B_{12}$ compared with participants without AMD ($P<0.05$) [19]. The risk of developing AMD was influenced by certain demographic factors or comorbidities. For example, the risk of AMD based on dietary intake of vitamins $B_1$, $B_2$, and $B_6$ differed in patients with versus without diabetes [19]. The between-group difference was notable for $B_6$, where the causal link was strongest in the diabetes subgroup [19]. For vitamin $B_9$, there appeared to be a modest effect of body mass index on AMD risk [19]. Lastly, a causal relationship between higher dietary vitamin $B_{12}$ intake and lower AMD risk was observed for men (OR 0.897 [95% CI 0.845–0.952]) but not for women (OR 1.014 [95% CI 0.928–1.107]) [19]. Zheng et al. evaluated the risk of developing early and late AMD in the NHANES population separately [18]. They reported an association between increased dietary intake of vitamin $B_1$ and lower risk of late AMD (adjusted OR 0.62 [95% CI 0.36–0.99]); however, no association was observed between dietary intake of vitamin $B_1$ and risk of early AMD (adjusted OR 1.11 [95% CI 0.88–1.40]) [18].

Although there was overall consistency that lower B vitamin intake or circulating concentrations were associated with increased risk of developing AMD, inconsistent results among studies may be related to differences in patient populations (e.g., geographic location, socioeconomic status, minimum age, lifetime diet), length of follow-up, stage of AMD (early, late/advanced, any), array of B vitamins measured, difficulty quantifying dietary intake of B vitamins based on diet, and cutoff values for vitamin levels that indicated low intake or deficiency.

## Progression of AMD

Data evaluating the potential association between B vitamins and AMD progression come from the longitudinal, observational component of the AREDS and AREDS2 studies [9, 10]. AREDS enrolled patients aged 55–80 years with drusen, noncentral geographic atrophy, or pigment abnormalities in one or both eyes, or who had advanced AMD or vision loss due to AMD in one eye [5]. Risk of progression to geographic atrophy decreased with higher dietary intake of vitamins $B_1$, $B_2$, and $B_9$ [9]. The association with vitamin $B_9$ intake remained significant after adjustment for covariates ($P<0.007$) [9]. A genetic influence was observed for the vitamin $B_9$ association, with a significantly lower risk of progression to geographic atrophy with increased dietary vitamin $B_9$ intake in patients who were homozygous for the complement component 3 R102G nonrisk allele (HR 0.43 [95% CI 0.27–0.70]; $P=0.0005$) [9].

A post hoc analysis explored associations between dietary nutrient intake and different forms of disease progression in a combined analysis of the AREDS and AREDS2 studies [10]. Whereas AREDS enrolled patients ranging from no AMD to unilateral late AMD, AREDS2 included patients with bilateral large drusen or unilateral late AMD [10]. Risk of progression to late AMD decreased with higher dietary intake of vitamins $B_6$ and $B_9$, risk of progression to geographic atrophy decreased with higher dietary

intake of vitamin $B_9$, and risk of progression to neovascular AMD nominally decreased with higher dietary intake of $B_6$ [10]. In a smaller cohort of patients from AREDS without large drusen or late AMD at baseline, the risk of progression to large drusen nominally decreased with greater dietary intake of vitamin $B_9$ [10].

Taken together, the observational AREDS and AREDS2 studies strongly support a protective effect of B vitamins to reduce the risk of AMD progression.

## B VITAMIN SUPPLEMENTATION: BRIDGING THE GAP

Given the difficulty many individuals face in achieving optimal nutrient intake through diet alone (Table 3) [21, 22], especially as nutrient absorption declines with age, targeted supplementation has emerged as a practical strategy to support ocular health and reduce the risk of AMD progression. A small number of studies have evaluated the effect of nutrient supplementation with B vitamin-containing supplements on AMD development or progression (Table 4) [23–30]. Differences in endpoint measures and composition of the supplements make it challenging to discern which, if any, effects are attributable to B vitamins. However, one study evaluated supplementation exclusively with B vitamins. The Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) enrolled women aged ≥ 40 years with preexisting cardiovascular disease or ≥ 3 cardiovascular risk factors and randomized them to treatment with vitamin B supplementation or placebo primarily to assess the effect on prevention of cardiovascular events [24]. The supplement contained vitamins $B_6$ (50 mg), $B_9$ (2.5 mg), and $B_{12}$ (1 mg) [24]. In a secondary analysis of the WAFACS data, daily vitamin B supplementation decreased the risk of developing AMD by 34% (relative risk [RR] 0.66 [95% CI 0.47–0.93]; $P = 0.02$) and the risk of developing visually significant AMD by 41% (RR 0.59 [95% CI 0.36–0.95]; $P = 0.03$) compared with placebo [24]. These data support a role for B vitamin supplementation in reducing the formation of AMD and suggest the need for

**Table 3** Dietary sources of vitamin B [21]

| Vitamin | Dietary sources |
|---|---|
| $B_1$ (thiamin) | Fortified cereals, fortified meat substitutes, grain products (e.g., whole grain bread), fruits (e.g., bananas, oranges), ham, liver,[a] nuts, peas, pork |
| $B_2$ (riboflavin) | Bread, eggs, fortified cereals, milk, mushrooms, yogurt |
| $B_3$ (niacin) | Eggs, fish, fortified cereals, liver,[a] meat, poultry, wheat flour, whole grain bread |
| $B_5$ (pantothenic acid) | Avocado, beef, broccoli, chicken, eggs, kidneys, liver,[a] mushrooms, oat cereals, potatoes, tomato products, whole grains, yeast |
| $B_6$ (pyridoxine) | Bananas, fish, fortified cereals, liver[a] and other organ meats, milk, oats, peanuts, pork, poultry, soy-based meat substitutes, soybeans, wheat germ |
| $B_7$ (biotin) | Widely distributed in natural foods, but concentration varies and generally not documented |
| $B_9$ (folate) | Beans and legumes, fortified cereals, fortified grain products, liver,[a] vegetables (e.g., broccoli, brussels sprouts, green beans, leafy green vegetables [e.g., cabbage, kale, lettuce, spinach, spring greens]) |
| $B_{12}$ (cobalamin) | Cheese, eggs, fortified cereals, fish (e.g., herring sardines, trout), game meat (venison, rabbit), organ meat (e.g., liver[a]), milk, shellfish |

Table created with data from the National Health Service [21] and Institute of Medicine of the National Academies [22]

[a]Should be avoided during pregnancy

**Table 4** Studies evaluating B vitamin supplementation in the development or progression of AMD

| Study | Study design | Population | Supplement composition and dose | Findings |
|---|---|---|---|---|
| Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) NCT00000541 (Christen 2009) [24] | Randomized, double-masked, placebo-controlled trial | Women aged ≥ 40 years with preexisting CVD or ≥ 3 CVD risk factors were randomized to vitamin B supplementation ($n = 2607$) or placebo ($n = 2598$) | Vitamin $B_6$: 50 mg/day<br>Vitamin $B_9$: 2.5 mg/day<br>Vitamin $B_{12}$: 1 mg/day | Daily vitamin B supplement significantly decreased the risk of developing AMD (RR 0.66 [95% CI 0.47–0.93]; $P = 0.02$) and the risk of developing visually significant AMD (RR 0.59 [95% CI 0.36–0.95]; $P = 0.03$) |
| AMD Study Group 1996 (AMD Study Group 1996; Richer 1996) [27, 28] | 18-month, prospective, double-masked, case–control study | Patients with atrophic AMD were randomized to treatment with Ocuguard® ($n = 39$) or placebo ($n = 32$)<br>Control group included age- and sex-matched patients without AMD ($n = 13$) | Vitamin $B_2$: 25 mg<br>Ocuguard also contains beta-carotene (20,000 IU), vitamin E (200 IU), vitamin C (750 mg), citrus bioflavonoid complex (125 mg), quercetin (bioflavonoid) (50 mg), bilberry extract (bioflavonoid) (5 mg), rutin (bioflavonoid) (50 mg), zinc picolinate (12.5 mg), selenium (50 µg), taurine (100 mg), *N*-acetyl cysteine (100 mg), L-glutathione (5 mg), and chromium (100 µg) | ↓ Dietary intake of vitamins $B_3$ and $B_9$ was observed in patients with atrophic AMD vs. controls<br>Supplementation stabilized but did not improve atrophic AMD<br>A slight cataractogenic effect was observed in patients who received the supplement |

**Table 4** continued

| Study | Study design | Population | Supplement composition and dose | Findings |
|---|---|---|---|---|
| Veterans LAST Study (Richer 2004; Richer 2007) [29, 30] | 12-month, prospective, randomized, double-masked, placebo-controlled trial | Patients treated at a Veterans Administration hospital who had atrophic AMD were randomized to treatment with lutein 10 mg ($n = 29$), a combination lutein/antioxidant/vitamin supplement (OcuPower®) ($n = 30$), or placebo ($n = 31$) | Vitamin $B_1$: 50 mg<br>Vitamin $B_2$: 10 mg<br>Vitamin $B_3$: 70 mg<br>Vitamin $B_5$: 50 mg<br>Vitamin $B_6$: 50 mg<br>Vitamin $B_{12}$: 500 µg<br>Folic acid ($B_9$): 800 µg<br>Biotin ($B_7$): 300 µg<br>OcuPower also contains lutein (10 mg), vitamin A (2500 IU), natural beta carotene (Betatenem) (15,000 IU), vitamin C (1500 mg), vitamin $D_3$(400 IU), vitamin E (500 IU), calcium (500 mg), magnesium (300 mg), iodine (75 µg), zinc (25 mg), copper (1 mg), manganese (2 mg), selenium (200 µg), chromium (200 µg), molybdenum (75 µg), lycopene (600 µg), bilberry extract (160 mg), alpha-lipoic acid (150 mg), *N*-acetyl cysteine (200 mg), quercetin (100 mg), rutin (100 mg), citrus bioflavonoids (250 mg), plant enzymes (50 mg), black pepper extract (5 mg), malic acid (325 mg), taurine (900 mg), L-glycine (100 mg), L-glutathione (10 mg), and boron (2 mg) | No progression to AMD retinopathy was observed in any treatment group<br>Increased macular pigment optical density and improved visual function was observed with lutein supplementation alone or the combination of lutein/antioxidant/vitamin supplementation |

Table 4 continued

| Study | Study design | Population | Supplement composition and dose | Findings |
|---|---|---|---|---|
| Pilot study (Falsini 2003) [23] | Nonrandomized, comparative clinical trial | Consecutive patients with bilateral early ARM were assigned to antioxidant supplementation ($n = 17$) or no treatment ($n = 13$) for 180 days<br>Age-matched controls were also treated with antioxidant supplementation ($n = 4$) or received no treatment ($n = 4$) | Nicotinamide ($B_3$): 18 mg/day<br>Also contains lutein (15 mg) and vitamin E (20 mg) | Patients with early ARM and age-matched controls who received antioxidant supplementation experienced statistically significant improvements in a measure of retinal function (FERG). No such changes were observed in untreated patients |
| 2011-A00922-39 NCT01404845 (Azar 2017) [25] | 24-month, prospective, randomized, double-masked, comparative, multicenter study | Consecutive patients without any retinal pathology who underwent cataract surgery and patients with stage 4 neovascular AMD were randomized to treatment with Nutrof® Total supplementation ($n = 64$) or noncarotenoid supplement (i.e., no lutein or zeaxanthin) placebo ($n = 62$) | Vitamin $B_6$: 2 mg<br>Vitamin $B_9$: 200 µg<br>Vitamin $B_{12}$: 1 µg<br>Nutrof Total also contains lutein (5 mg), zeaxanthin (1 mg), omega-3 FA (DHA 560 mg, GLA 420 mg), vitamin C (80 mg), vitamin E (10 mg), and zinc (10 mg) | No statistically significant increase in macular pigment optical density was observed in patients with or without AMD regardless of treatment group |

**Table 4** continued

| Study | Study design | Population | Supplement composition and dose | Findings |
|---|---|---|---|---|
| RET 04 2017<br>NCT03919019<br>(Parravano 2019) [26] | Randomized, double-masked, monocentric, morpho-functional study | Patients with intermediate AMD (AREDS category 3 features) were randomized to Macuprev® ($n = 15$) or placebo ($n = 15$) | Vitamin $B_{12}$: 18 mg/day<br>Macuprev also contains lutein (20 mg), zeaxanthin (4 mg), *N*-acetyl cysteine (140 mg), bromelain 2500GDU (80 mg), vitamin $D_3$ (800 IU), alpha-lipoic acid (140 mg), rutin (157 mg), vitamin C (160 mg), zinc oxide (16 mg), *Vaccinium myrtillus* 36% anthocyanosides (90 mg), and *Ganoderma lucidum* (600 mg) | Functional improvement of preganglionic retinal elements was observed after 6 months in patients who received supplementation<br>Macular chorioretinal structural parameters were unchanged at follow-up in the supplement group<br>In the placebo group, no functional or structural changes were observed |

*AMD* age-related macular degeneration, *AREDS* Age-Related Eye Disease Study, *ARM* age-related maculopathy, *CVD* cardiovascular disease, *DHA* docosahexaenoic acid, *FA* fatty acid, *FERG* focal electroretinogram, *GDU* gelatin digestion unit, *GLA* gamma-linolenic acid, *IU* international unit, *RR* relative risk

further evaluation of B vitamin supplementation as an adjunct to existing formulations, such as AREDS and AREDS2, that have been proven to reduce the risk of AMD progression. It is important to note that the levels of $B_6$, $B_9$, and $B_{12}$ in the WAFACS study were relatively high compared to the levels in the typical B complex vitamin formulations currently available. The vitamin B levels in the WAFACS study were the basis for the concentrations chosen for intervention in AREDS3, which supports the argument that just supplementing AREDS2 with an existing vitamin B complex may not be sufficient for reducing the risk of AMD development and progression. Furthermore, AREDS2 supplementation most frequently targets patients with intermediate-stage AMD; therefore, addition of a high-dose vitamin B complex to the AREDS2 formulation could extend the benefit to patients with early-stage AMD.

## HYPOTHESIZED MECHANISMS FOR B VITAMIN-MEDIATED PROTECTION IN AMD

One proposed mechanism by which B vitamins influence AMD risk is through lowering homocysteine levels (Fig. 1) [7, 31–43]. Homocysteine induces oxidative stress, which has multiple damaging effects on retinal health, including altering retinal pigment epithelium (RPE) structure and function and promoting inflammatory processes [31, 33, 44]. The metabolism of homocysteine requires vitamins $B_6$, $B_9$, and $B_{12}$ [31, 44]. Under conditions of vitamin insufficiency, homocysteine concentrations rise [44]. In contrast, higher dietary consumption or supplementation of B vitamins is linked to lower homocysteine levels [32, 45, 46]. B vitamins play a key role in DNA methylation through one-carbon metabolism; deficiency of these nutrients can therefore lead to epigenetic changes in expression of disease-related factors [11, 20].

Observational studies have shown that serum total homocysteine concentration is higher in patients with versus without AMD (Table 2) [8, 12, 13, 17, 20]. In their 2014 systematic review and meta-analysis of 11 case–control studies, Huang et al. found that average serum total homocysteine concentrations were significantly greater for patients with AMD than in control groups without AMD ($P<0.00001$) [8]. These findings were affirmed by a subsequent meta-analysis of 10 case–control studies of patients with neovascular AMD conducted by Pinna et al. [20]. Interestingly, greater serum total homocysteine in patients with neovascular AMD versus all AMD was observed in the Huang et al. meta-analysis [8].

In addition to improving RPE health via downregulating homocysteine levels, B vitamins ($B_2$ and $B_3$ derivative nicotinamide) have been shown to play a role in suppressing RPE epithelial to mesenchymal transition, a process associated with vision-impairing clinical conditions [35, 36]. Treatment with the vitamin $B_3$ derivative nicotinamide has been shown to suppress AMD/drusen-associated protein production, complement and inflammatory pathways, and vascular endothelial growth factor A (VEGF-A) production [37]. Further, supplementation of vitamin $B_3$ (niacin) improved choroidal blood volume in patients with AMD, attributable to the vasodilatory property of niacin [41].

Another proposed mechanism for AMD-related protective effects of B vitamins is through enhancing mitochondrial metabolism. The RPE relies heavily on mitochondrial metabolism [39], which may be compromised in patients with AMD as result of a reduction in the number of mitochondria and alterations in the mitochondrial genome [47]. B vitamins, including $B_1$, $B_2$, $B_3$, $B_5$, $B_7$, $B_9$, and $B_{12}$, are essential to normal mitochondrial function [48]. Evidence from preclinical studies suggests that B vitamin supplementation enhances mitochondrial metabolism [39].

## CONCLUSIONS

B vitamins have the capacity to counteract several mechanisms believed to be involved in the pathogenesis of AMD, including oxidative stress, mitochondrial dysfunction, and inflammatory activation. Emerging evidence highlights the potential role of B vitamins (especially $B_6$, $B_9$,

and $B_{12}$) in reducing the risk of AMD development and progression. Data from large observational studies and clinical trials spanning many years confirm the association between low dietary intake of or deficiency in B vitamins and increased risk of AMD. Moreover, evidence supports increasing vitamin B intake to reduce the risk of AMD development and progression. The introduction of a supplement that combines the established efficacy of an antioxidant vitamin/mineral/carotenoid formulation with high-dose B vitamins has the potential to offer a new option for clinicians and their patients to reduce the risk of AMD progression.

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### *Declarations*

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***Ethical Approval.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

***Conflict of Interest.*** Julie Poteet reports serving on advisory boards for Bausch + Lomb. Cecelia Koetting reports serving as a speaker, consultant, researcher, and/or advisor for AbbVie, Alcon, Allergan, Azura Ophthalmics, Bausch + Lomb, Blinkjoy, Bruder Healthcare, Dompé, Myze, Orasis Pharmaceuticals, RVL Pharmaceuticals, Sight Sciences, Tarsus Pharmaceuticals, Théa Pharma, Trukera Medical, Twenty/Twenty Therapeutics, and Viatris. Priya S. Vakharia reports serving as an investigator for Alexion Pharmaceuticals, Allgenesis Biotherapeutics, Aviceda Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Kirwin, Kodiak Sciences, Kyoto Pharmaceutical Industries, Ocular Therapeutix, OcuTerra Therapeutics, Opthea, ONL Therapeutics, Recens Medical, Regenx Bio, Stealth BioTherapeutics, and Unity; a consultant for AbbVie, Alimera Sciences, Annexon Biosciences, Apellis Pharmaceuticals, Astellas Pharma, Bausch + Lomb, Bayer, Coherus, Genentech, Notal Vision, Novartis, Ocuphire Pharma, and Regeneron Pharmaceuticals; a speaker for Astellas Pharma, Bausch + Lomb, Genentech, Heidelberg, and Regeneron Pharmaceuticals; and being an equity/stockholder in Quad-C/Prism.



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