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Ophthalmic Technology Assessment

Dietary Supplementation for Retinitis Pigmentosa

A Report by the American Academy of Ophthalmology

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Purpose: To review the evidence on the effectiveness of dietary supplementation for retinitis pigmentosa (RP).

Methods: A literature search of the PubMed database was last conducted in January 2024 to identify published English-language original research on dietary supplementation for RP. Eligible compounds included products ingested orally containing nutrients intended to supplement the diet. Studies meeting eligibility criteria were assigned a level of evidence rating by the panel methodologist.

Results: The search identified 283 citations, 15 of which met the assessment criteria. Two studies were rated level I, 11 studies were rated level II, and 2 studies were rated level III. All were single-center studies and were published between 1993 and 2022. The products evaluated included vitamin A, docosahexaenoic acid (DHA), lutein, vitamin E, goji berry (*Lycium barbarum* fruit) extract, and chlorogenic acid. Primary outcome measures were most commonly based on electroretinography (n = 7) or perimetry (n = 2) testing. Numerous studies highlighted data suggestive of possible efficacy for vitamin A, DHA, and lutein, yet these findings typically derived from secondary outcomes, evaluations of participant subsets, post hoc analyses, problematic interpretations of the data, or a combination thereof. Additionally, it was often unclear if the study findings represented clinically meaningful outcomes. No prominent safety concerns were reported in any study.

Conclusions: No high-quality evidence was found to support the effectiveness of any form of dietary supplementation for RP. The findings underscore the challenges of studying this rare and slowly progressive retinal disease. Future studies should leverage the enhanced recruitment abilities from collaborative research networks to refine eligibility criteria while using novel, clinically meaningful endpoints.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The information in this assessment is valid at the time of publication. Each assessment is reviewed for currency by its panel every 5 years, and the panel decides whether to maintain, revise, or retire the assessment. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Retina/Vitreous Panel was to review the evidence on the effectiveness of dietary supplements on disease progression in retinitis pigmentosa (RP).

Background

Retinitis pigmentosa is the most common monogenic inherited retinal disease (IRD) worldwide, with an estimated prevalence of 1 in 4000.[1] Individuals with RP experience nyctalopia, peripheral visual field loss, and eventually central vision loss, with legal blindness often developing in the later stages of disease. Disease-causing mutations in

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approximately 100 genes may lead to the diffuse rod–cone pattern of photoreceptor degeneration observed in RP.[2] Currently, the only available United States Food and Drug Administration (FDA)-approved therapy for RP is voretigene neparvovec-rzyl, a gene augmentation product for retinal degeneration associated with biallelic mutations in the *RPE65* gene.[3] Variants in this gene account for disease in less than 1% of individuals with RP[1,4]; no FDA-approved therapy is available for individuals impacted by other forms of RP.

Nutritional approaches have long been studied for management of retinal degenerative diseases, perhaps best exemplified by the Age-Related Eye Disease Study supplements for age-related macular degeneration.[5] For IRDs, a plausible biological rationale seems to exist for nutritional supplementation. The retina is enriched in diet-derived compounds, such as lutein and omega-3 fatty acids, and vitamin A is a precursor to the chromophore that initiates phototransduction. Oxidative stress and inflammation in the metabolically active retina may contribute to the progressive degeneration in IRDs, and nutritional supplements may provide antioxidant and anti-inflammatory benefits. Furthermore, dietary supplementation offers the promise of being a widely available, potentially gene-agnostic approach for treating this genetically diverse category of diseases.

Numerous clinical studies have evaluated the role of dietary supplementation in RP. In particular, a clinical trial initiated in 1984 explored the role of high-dose vitamin A supplementation in slowing disease progression in RP.[6] However, questions about the study's conclusions arose soon after publication,[7] and no consensus about best practice exists.[8] The aim of this assessment was to evaluate evidence for dietary supplementation in RP to provide guidance to clinicians on best practices for managing this condition.

Food and Drug Administration Status

According to the Dietary Supplement Health and Education Act amendment to the Federal Food, Drug, and Cosmetic Act, the FDA does not have the authority to approve dietary supplements for safety and effectiveness or to approve their labeling before such products are marketed to the public. Because of the less stringent regulatory framework, some authors have raised concerns about the quality of marketed supplements, although this issue is out of the scope of the current assessment.[9]

Question for Assessment

The focus of this assessment is to address the following question: Does dietary supplementation slow disease progression compared with placebo or observation in patients with RP? Eligible compounds that were considered included products ingested orally containing nutrients (such as vitamin A, omega-3 fatty acids, and lutein) intended to supplement the diet.[10]

Description of Evidence

A literature search of the PubMed database was last conducted in January 2024. No date restrictions were imposed, and the search was limited to studies published in English. Search terms for this assessment can be found in the Appendix (available at www.aaojournal.org).

The combined searches yielded 283 citations, and the panel reviewed the full text of 31 articles. Of these, 15 articles met the following eligibility criteria: (1) the research was original; (2) the study evaluated the impact of dietary supplementation on disease progression among humans with RP; (3) outcome measures included visual acuity (VA), perimetry, full-field electroretinography, OCT, or a combination thereof; and (4) follow-up duration was at least 3 months. Eligible study populations included adults and children with RP without known nutritional deficiencies.

All studies were single-center studies and were published between 1993 and 2022. One article using multiple simultaneous interventions in the treatment arm, including dietary supplements, was excluded because it is not possible to evaluate the effect of the supplements alone.[11] Another article that presented a reanalysis of an included study is discussed, but is not included formally in this assessment.[12]

The panel methodologist (M.G.M.) assessed the study design of 15 studies and rated each for strength of evidence according to the guidelines adopted by American Academy of Ophthalmology, which are based on the 2011 rating scale developed by the Oxford Centre for Evidence-Based Medicine.[13] A level I rating was assigned to well-designed and well-executed randomized controlled trials and systematic reviews, a level II rating was assigned to cohort studies and nonrandomized controlled cohort or follow-up trials, and a level III rating was assigned to case series and case-controlled studies and reports based on inferences. Studies may be downgraded or upgraded based on study quality as well as effect size according to the rating guidelines.[13] Two articles were rated level I, 11 articles were rated level II, and 2 articles were rated level III.

Published Results

The 15 studies included in this assessment are summarized in Table 1 and are grouped according to intervention. Effect size and confidence intervals (CIs), if not directly reported, were computed when possible, using data available within the articles. Because the precision of the reported standard deviations or standard errors of estimates was not high in some articles, the CIs may not correspond exactly with cited *P* values.

Vitamin A and Associated Compounds

Vitamin A, in conjunction with the photoreceptor opsin protein, serves as the retinal chromophore that initiates phototransduction.[14] Among individuals with an otherwise healthy retina, vitamin A deficiency leads to nyctalopia and ultimately to structural changes to the outer retina.[15,16] Some clinicians have posited that high-dose vitamin A supplementation may slow photoreceptor degeneration in

Table 1. Summary of Included Studies

Author(s) (Year)	Level of Evidence	Design endpoints	Disease	No. of Participants Enrolled/ Randomized	No. of Participants in Primary Analysis	Study Groups	Duration	Primary Outcome Measure	Result for Primary Outcome	Secondary Outcome Measure(s)	Safety
Vitamin A and related compounds											
Berson et al (1993)[6]	II	RCT	RP	601	601 (472 with data to 5 yrs, 261 with data to 6 yrs)	1. Vitamin A 15 000 IU/day plus trace vitamin E 2. Vitamin A 15 000 IU/day plus vitamin E 400 IU/day 3. Vitamin A and vitamin E trace amounts 4. Vitamin E 400 IU/day plus trace vitamin A	4–6 yrs	ERG: photopic flicker amplitude	Approximate mean annual amplitude loss, 6.2% (high-dose vitamin A) vs. 7.5% (control); $P = 0.01$	ETDRS BCVA; Goldmann VF: area using V4e stimulus	"No systemic illness or toxicity"
Rotenstreich et al (2013)[27]	II	RCT with crossover	RP	34	29 (per-protocol analysis)	1. Alga containing β-carotene (approximately 20 mg/day) 2. Placebo	9 mos (3 mos in each arm with 3-mo washout)	ERG: maximal scotopic b-wave amplitude	Mean amplitude change, +8.4 μV (β-carotene) vs. −5.9 μV (placebo) Mean difference, 14.3 μV (95% CI, 8.8–19.8 μV; $P = 0.001$)	ERG: photopic b-wave amplitude; Goldmann VF: dark-adapted chromatic field areaand "Conventional" light-adapted VF area; ETDRS BCVA	Not reported
Berson et al (2018)[20]	II	Retrospective cohort study	Children with RP	80	80	1. High-dose vitamin A supplementation (n = 55; self-report) 2. Control (n = 25)	Varied	ERG: photopic flicker amplitude	Approximate mean annual amplitude loss, 6.9% (high-dose vitamin A) vs. 13.2% (control) Mean difference in exponential rate of change, 0.0706 $\log_e$-unit per year (95% CI, 0.0149–0.1263 $\log_e$-unit per year; $P = 0.01$)	VF area, VA	No adverse events (participant- and family-reported)

Table 1. (Continued.)

Author(s) (Year)	Level of Evidence	Design endpoints	Disease	No. of Participants Enrolled/ Randomized	No. of Participants in Primary Analysis	Study Groups	Duration	Primary Outcome Measure	Result for Primary Outcome	Secondary Outcome Measure(s)	Safety
Docosahexaenoic acid											
Berson et al (2004)[32]	I	RCT	RP	221	205	1. DHA 1200 mg/ day plus vitamin A 15 000 IU/day 2. Placebo plus vitamin A 15 000 IU/day	4 yrs	HVF: 30-2 total point score (size V target)	Mean annual sensitivity loss, 37 dB (DHA plus vitamin A) vs. 38 dB (vitamin A) Mean difference, 0.73 dB (95% CI, −9.98 to 8.52 dB; P = 0.88)	HVF: total point score for 30-2 and 30/60-1 programs; ERG: photopic flicker amplitude	None
Berson et al (2004)[33,*]	II	Cohort study (subgroup analysis of Berson et al [2004][32] RCT)	Subgroups of participants with RP either receiving (n = 143) or not receiving (n = 65) vitamin A before study entry	221	N/A	1. DHA 1200 mg/ day plus vitamin A 15 000 IU/day 2. Placebo plus vitamin A 15 000 IU/day	4 yrs	N/A (subgroup analysis)	N/A	HVF: 30-2 total point score and total point score for 30-2 and 30/ 60-1 programs combined; ETDRS BCVA; ERG: photopic flicker amplitude	None
Hoffman et al (2004)[34]	II	RCT	Male patients with XLRP	44	44 (intent-to-treat analysis)	1. DHA 400 mg/day 2. Placebo	4 yrs	ERG: photopic flicker amplitude	Mean log amplitude loss, −0.199 μV (DHA) vs. −0.266 μV (placebo) Mean difference, 0.07 log μV (95% CI, −0.43 to 0.57 log μV; P = 0.20)	ETDRS BCVA; HVF: 30-2 and 30/60-2 mean field defect; dark-adapted visual threshold; fundus photograph grading; visual activities questionnaire	"No major adverse events"

(*Continued*)

Table 1. (Continued.)

Author(s) (Year)	Level of Evidence	Design endpoints	Disease	No. of Participants Enrolled/ Randomized	No. of Participants in Primary Analysis	Study Groups	Duration	Primary Outcome Measure	Result for Primary Outcome	Secondary Outcome Measure(s)	Safety
Hoffman et al (2014)[36]	II	RCT	Male patients with XLRP	78	60 (modified intent-to-treat analysis)	1. DHA 30 mg/kg per day plus multivitamin 2. Placebo plus multivitamin	4 yrs	ERG: photopic flicker amplitude	Mean annual amplitude loss, 0.028 log μV/y (DHA) vs. 0.022 log μV/y (placebo) Mean difference, −0.006 log μV/y ($P = 0.30$)	ERG: maximum scotopic b-wave amplitude and implicit times	"No severe treatment-emergent adverse events requiring hospitalization." "27 participants had a total of 42 related or possibly related treatment-emergent adverse events."
Hoffman et al (2015)[37,*]	II	RCT (secondary analyses of Hoffman et al [2014][36])	Male patients with XLRP	78	51 (prespecified per-protocol analysis)	1. DHA 30 mg/kg per day plus multivitamin (n = 29) 2. Placebo plus multivitamin (n = 22)	4 yrs	N/A (secondary outcomes)	N/A	HVF summed point scores using 30-2 and 60-2 grids (size V stimulus); ETDRS BCVA; dark-adapted threshold; shape discrimination threshold; color fundus photograph disease progression grade; ellipsoid zone width constriction	"No severe treatment-emergent adverse events requiring hospitalization." "27 participants had a total of 42 related or possibly related treatment-emergent adverse events."
Berson et al (2012)[39,*]	II	Cohort study (secondary analysis of aggregated trial data)	RP	357	357	1. Omega-3 fatty acids ≥ 0.20 g/day (estimated dietary intake; n = 215) 2. Omega-3 fatty acids < 0.20 g/day (estimated dietary intake; n = 142)	4–6 yrs	N/A (secondary data analysis)	N/A	ETDRS VA; potential acuity meter retinal acuity; ERG: photopic flicker amplitude (n = 266)	N/A (observational study)

Table 1. (Continued.)

Author(s) (Year)	Level of Evidence	Design endpoints	Disease	No. of Participants Enrolled/ Randomized	No. of Participants in Primary Analysis	Study Groups	Duration	Primary Outcome Measure	Result for Primary Outcome	Secondary Outcome Measure(s)	Safety
Lutein											
Berson et al (2010)[40]	I	RCT	RP	240	215	1. Lutein 12 mg/day plus vitamin A 15 000 IU/day 2. Placebo plus vitamin A 15 000 IU/day	4 yrs	HVF 30-2 total point score	Mean annual rate of sensitivity loss, 49.6 dB/yr (lutein plus A) vs. 51.5 dB/yr (control plus A) Mean difference, −1.9 dB/yr (95% CI, −10.7 to 6.9 dB/yr; P = 0.66)	HVF 60-4 total point score and combined HVF 30-2 plus HVF 60-4 total point score; ERG: photopic flicker amplitude; ETDRS VA	"No evidence of systemic illness or toxicity." 2 withdrawals from treatment arm because of elevated LFT results
Bahrami et al (2006)[43]	II	RCT with crossover	RP	45	34 (per-protocol analysis)	1. Lutein 10 mg/day then 30 mg/day 2. Placebo	48 wks (crossover at 24 wks)	N/A (secondary outcomes)	N/A	PC-based VA; PC-based central visual field; PC-based contrast sensitivity	"No significant adverse events"
Dagnelie et al (2000)[44]	III	Cohort study	RP and other inherited retinal diseases	20	16	1. Lutein 40 mg/day then 20 mg/day 2. Lutein 40 mg/day then 20 mg/day plus DHA 500 mg/day plus vitamin B complex plus digestive enzymes	26 wks	PC-based VA	Mean VA improvement, 0.7dB (P < 0.05) for entire cohort	VF measured at home; visual function questionnaire	Not reported
Vitamin E											
Berson et al (1993)[6]	II	RCT	RP	601	601 (472 with data to 5 yrs, 261 with data to 6 yrs)	1. Vitamin A 15 000 IU/day 2. Vitamin A 15 000 IU/day plus vitamin E 400 IU/day 3. Vitamin A and vitamin E trace amounts 4. Vitamin E 400 IU/day	4–6 yrs	ERG: photopic flicker amplitude	No significant difference (P = 0.45) between groups (primary analysis)	ETDRS BCVA; Goldmann VF: area using V4e stimulus	"No systemic illness or toxicity"

(*Continued*)

Table 1. (Continued.)

Author(s) (Year)	Level of Evidence	Design endpoints	Disease	No. of Participants Enrolled/ Randomized	No. of Participants in Primary Analysis	Study Groups	Duration	Primary Outcome Measure	Result for Primary Outcome	Secondary Outcome Measure(s)	Safety
***Lycium barbarum* extract**											
Chan et al (2019)[45]	II	RCT	RP	50	42	1. *L. barbarum* extract 5 g/day 2. Placebo	1 yr	High- and low-contrast ETDRS BCVA	12-mo change in high-contrast VA, −0.02 ± 0.09 logMAR (treatment) vs. 0.11 ± 0.17 logMAR (placebo; P = 0.001) 12-mo change in low-contrast VA, −0.06 ± 0.08 logMAR (treatment) vs. 0.11 ± 0.16 logMAR (placebo; P = 0.001)	ERG: scotopic max b-wave amplitude, photopic a-wave amplitude, andphotopic b-wave amplitude; HVF: 30-2 mean deviation; OCT: center point thickness	"No significant adverse effects"
Chlorogenic acid											
Shin and Yu (2014)[47]	III	Cohort study	RP	18	18	1. Chlorogenic acid 60 mg/day	3 mos	Multifocal ERG: ring amplitudes (rings 1−5)	Mean mfERG ring 5 amplitude, 7.2 μV (before treatment) vs. 8.3 μV (after treatment) Mean difference, 1.1 μV (P = 0.022; no significant finding for rings 1−4)	HVF: total point score (size III stimulus, grid not specified); ERG: "rod response amplitude", "combined response amplitude", and single flash cone response amplitude; contrast sensitivity; ETDRS BCVA	"No systemic adverse events"
Antioxidant complex											

Table 1. (Continued.)

Author(s) (Year)	Level of Evidence	Design	endpoints	Disease	No. of Participants Enrolled/ Randomized	No. of Participants in Primary Analysis	Study Groups	Duration	Primary Outcome Measure	Result for Primary Outcome	Secondary Outcome Measure(s)	Safety
Olivares-Gonzalez et al (2022)[46]	II	RCT		RP	31	25	1. Nutrient complex (folic acid, vitamin B6, vitamin A, zinc, copper, selenium, lutein, zeaxanthin) 2. Placebo	2 yrs	Multifocal ERG: summed P1 response amplitude	Mean sum mfERG amplitude (± SD) at baseline and 2 yrs, 10.06 ± 4.33 nV/deg^2 and 11.82 ± 3.05 nV/deg^2 for treatment arm; and 10.38 ± 5.91 nV/deg^2 and 8.89 ± 3.80 nV/deg^2 for placebo arm	HVF: summed point score OCT: macular thickness within ETDRS grid sectors	Not reported

BCVA = best-corrected visual acuity; CI = confidence interval; DHA = docosahexanoic acid; ERG = electroretinography; ETDRS = Early Treatment Diabetic Retinopathy Study; HVF = Humphrey visual field; IU = international units; LFT = liver function test; logMAR = logarithm of the minimum angle of resolution; mfERG = multifocal electroretinography; N/A = not applicable; PC = personal computer; RCT = randomized controlled trial; RP = retinitis pigmentosa; VA = visual acuity; VF = visual field; XLRP = X-linked retinitis pigmentosa.
*Article reports ancillary outcomes of another included study.

RP. Three level II studies assessed the impact of supplementation with vitamin A and related compounds in patients with RP.

Berson et al[6] conducted what is perhaps the most recognized study at a single site in Boston, Massachusetts, from 1984 through 1991. In this level II study, the authors enrolled 601 participants with RP, randomized to high-dose (15 000 IU retinyl palmitate daily) vitamin A supplementation versus a control group receiving trace vitamin A supplementation. Using a 2 × 2 factorial design, the study also evaluated the role of vitamin E supplementation (see below). Participants receiving high-dose vitamin A showed a statistically significant reduction in the annual rate of amplitude loss in the 30-Hz photopic flicker electroretinography response (approximately 6.2% vs. 7.5% [$P = 0.01$] for high-dose vitamin A vs. trace vitamin A, respectively, among all randomized participants). The authors did not find significant differences among the secondary endpoints evaluating visual field (VF) progression or VA loss. The authors reported no safety concerns from high-dose vitamin A supplementation.

Several methodologic limitations raise questions about the validity of the authors' conclusions that the results supported a beneficial effect of vitamin A supplementation. First, although the primary endpoint was intended to be measured at 4 years, the authors included data for participants that remained in the study beyond this time point, including 472 participants at 5 years and 261 participants at 6 years. Rather than report raw amplitude data, the authors estimated the rate of electroretinography amplitude change over time, and the purported treatment effect seemed to be driven by the subgroup of participants with 6-year data. Additionally, the use of electroretinography amplitudes as a primary endpoint has limitations. It is unclear whether the slight observed impact on this measure of retinal function was clinically relevant, particularly considering the null result with the VF and VA endpoints. Prior studies have suggested that a flicker-response amplitude reduction of 37% is required to establish disease progression in an individual with RP.[17,18] Furthermore, the mean baseline 30-Hz electroretinography amplitude among all participants in this study was in the submicrovolt range, a small response that may be vulnerable to testing artifact and intertest variability, although the authors have asserted success with low-amplitude measurements in their electroretinography laboratory.[19] With respect to the factorial design, the analysis assumed no interaction effect between the vitamins A and E interventions, although it is unclear from the data presented if an interaction was present. Finally, the authors did not adjust for multiple comparisons in their analyses.

A 2023 study performed additional analyses of this trial data and did not replicate findings suggesting a beneficial vitamin A treatment response.[12] The authors performed multiple new analyses, including evaluating data only up to year 4 for all participants; expanding the 5- and 6-year dataset by including visits from after the original datalock; expanding the treatment arm using additional participants from a subsequent trial; and adjusting for baseline 30-Hz implicit time, a biomarker strongly associated with

progression rate, which coincidentally was imbalanced among the study arms at baseline. None of these analyses demonstrated a treatment effect for vitamin A.

A level II retrospective cohort study of vitamin A supplementation in children with RP recorded 30-Hz flicker electroretinography amplitudes among 70 children evaluated between 1976 and 2016.[20] The authors observed a lower rate of decline of 30-Hz flicker electroretinography amplitudes among patients who self-reported taking age-based vitamin A supplementation in a dose ranging from 5000 to 15 000 IU/day. The estimated mean annual rate of decline was 6.9% in the vitamin A group versus 13.2% in the control group ($P = 0.01$); the difference in mean exponential rate of change was 0.0706 $\log_e$-unit per year (95% CI, 0.0149−0.1263 $\log_e$-unit per year). Again, no significant difference was noted among secondary endpoints of VF area and VA, raising the question of clinical significance of the electroretinography changes. Additionally, given the retrospective nature of this study and self-selection for vitamin A use, potential for residual confounding was present.

Although these studies did not raise safety concerns with vitamin A supplementation, excess vitamin A intake may lead to both acute and chronic toxicity. Of note, the high daily dose of 15 000 IU retinyl palmitate, a retinol ester, exceeds the 2018 FDA-recommended tolerable upper intake level for adult men (approximately 10 000 IU of retinol daily).[21] Chronic excessive vitamin A intake has been associated with liver abnormalities, reduced bone density, and increased intracranial pressure. Some groups may be at increased risk of hip fracture.[22–24] Women of childbearing age should not take excess vitamin A because of teratogenicity involving cranial neural crest cells in the developing fetus.[25,26] Children, the elderly, and patients with liver disease, hyperlipidemia, high alcohol intake, or a combination thereof are other groups who may be particularly susceptible to vitamin A toxicity.

A 2013 level II randomized controlled trial evaluated supplementation with a 9-cis-β-carotene-rich powder derived from the alga *Dunaliella bardawil*.[27] β-Carotene is a dietary carotenoid that serves as a vitamin A precursor and may play an antioxidant role in the retina. The authors of this study hypothesized that the specific 9-cis-β-carotene isomer that is enriched in this algal product may benefit eyes with retinoid cycle dysfunction, supplying precursor for an active 9-cis retinal photopigment without the need for isomerization. This 9-month randomized, placebo-controlled, crossover-design study enrolled 34 participants, with 3 months each of placebo and β-carotene treatment (approximately 20 mg β-carotene daily) and a 3-month intervening washout period. The study demonstrated a statistically significant improvement in the primary efficacy endpoint of the scotopic maximal electroretinography b-wave amplitude (+8.4 μV in the β-carotene group vs. −5.9 μV in the control group; $P = 0.001$; mean difference, 14.3 μV [95% CI, 8.8−19.8 μV]). The study did not find a significant impact on VF or VA endpoints. The authors performed a per-protocol analysis, excluding the 5 participants (15%) who did not complete the study. Placebo resulted in a 15.9% decline in electroretinography response amplitude over 3 months, notably higher than what is observed in natural history studies of this disease. As discussed above, electroretinography endpoints should be interpreted cautiously given uncertainty about the clinical significance of findings as well as the potential for intertest variability. Finally, although this study did not identify prominent safety concerns, β-carotene supplementation at 20 to 30 mg daily has been associated with an increased risk of lung and gastric cancer among those who smoke and asbestos workers.[28,29]

Docosahexanoic Acid

Docosahexanoic acid (DHA) is an omega-3 fatty acid that is enriched among the phospholipids that comprise retinal membranes, including photoreceptor outer segments and rod disc membranes.[30] This highly unsaturated compound supports membrane fluidity and may impact phototransduction.[31] Six studies addressed DHA in RP, 3 of which reported primary analyses of 3 distinct randomized controlled trials. The other 3 studies reported secondary or subgroup analyses of trial data.

A level I 2004 single-center randomized controlled trial evaluated 221 participants with RP of all inheritance patterns randomized 1:1 to either 1200 mg DHA plus 15 000 IU vitamin A daily or placebo plus 15 000 IU vitamin A daily.[32] The primary endpoint measured at 4 years was the total point score on 30-2 Humphrey visual field (HVF) testing using a size V target. Secondary outcome measures included the 30-Hz photopic flicker amplitude, Early Treatment Diabetic Retinopathy Study (ETDRS) VA, and additional perimetry measures. No statistically significant difference was observed between the two study arms across any endpoint, by both intention-to-treat and per-protocol analyses (n = 208). The mean annual rate of total point score decline was 36.95 dB and 37.68 dB for the DHA plus vitamin A group and placebo plus vitamin A group, respectively, with a mean difference of 0.73 dB (95% CI, −9.98 to 8.52 dB; $P = 0.88$). No safety concerns were observed. This study was particularly well designed and executed with a relatively large number of participants, high retention across 4 years, double masking, block randomization stratified by dietary DHA intake and genotype, and careful eligibility criteria and analyses to limit the impact of floor effects.

An additional level II study reported post hoc subgroup analyses from the same 2004 randomized controlled trial and evaluated the potential impact of vitamin A supplementation before study enrollment.[33] The authors noted that 70% of participants in each treatment arm had been taking vitamin A 15 000 IU before enrollment and made an unanticipated observation at year 1 that the DHA plus vitamin A arm fared better than the placebo plus vitamin A arm among the minority of participants who were not taking vitamin A at study entry. Among this subgroup not taking vitamin A before the study (n = 65), the mean annual rate of decline of total point score on HVF 30-2 testing was 31 dB and 53 dB for the DHA plus vitamin A group and the control plus vitamin A group, respectively, with a mean difference of −22 dB (95% CI, −39.3 to

−4.2 dB; $P = 0.01$). Significant effects also were observed for the total VF (30-2 and 30/60-1 grids) and 30-Hz electroretinography flicker response endpoints. Caution should be exercised in interpreting these post hoc subgroup results, especially in the context of the null result across all the prespecified study endpoints. Notably, the difference in outcomes observed at 4 years primarily reflected the unexpected divergence at year 1. Additionally, among this subgroup of participants not taking vitamin A at baseline, the DHA plus vitamin A group had baseline HVF scores that trended lower than those of the placebo plus vitamin A group, possibly impacting the rate of subsequent VF loss.

In a level II 2004 randomized controlled trial,[34] 44 male patients with X-linked RP were randomized 1:1 to 400 mg DHA daily versus placebo and followed annually for 4 years. Individuals with mutations in both the *RPGR* and *RP2* genes were eligible. The primary endpoint was photopic 31-Hz flicker electroretinography response amplitude. The authors also reported ETDRS best-corrected VA, static perimetry using an HVF 30-2 testing grid, final dark-adapted visual threshold, fundus photograph grading, and patient-reported outcomes using the Visual Activities Questionnaire.[35] The authors found no statistically significant difference in the primary endpoint of cone amplitude at 4 years ($P = 0.16$) with an approximate mean difference of 0.07 log μV (95% CI, −0.43 to 0.57 log μV), but concluded that the study might have been underpowered and that the DHA dose may be optimized further. A supplemental analysis demonstrated a significant inverse association between erythrocyte DHA content, which may reflect study drug compliance, and rate of flicker amplitude loss. No serious adverse events were reported.

In a subsequent level II 2014 randomized controlled trial by the same authors, 78 male patients with X-linked RP were randomized 1:1 to DHA or placebo and followed for 4 years.[36] Based in part on findings from the prior study, the DHA dose was higher, and weight based at 30 mg/kg per day, with the daily dose ranging from 600 to 3600 mg. The primary outcome was rate of decline of photopic flicker electroretinography amplitude, and secondary outcomes included scotopic electroretinography response amplitudes and implicit times. Notably, 18 patients (23%) withdrew from the study, and a modified intention-to-treat analysis was performed. This study yielded no significant difference between groups among any of the electroretinography endpoints (flicker amplitude decline of 0.028 log μV/year DHA vs. 0.022 log μV/year placebo; $P = 0.30$; mean difference, −0.006 log μV/year) despite demonstrating a mean 4-fold elevation of red blood cell DHA content in the treatment arm. The authors noted that the placebo arm exhibited a lower than anticipated rate of electroretinography amplitude loss. No prominent safety issues were reported.

An additional paper reported level II data on numerous ancillary outcomes from the same 2014 randomized controlled trial using a prespecified per-protocol analysis for the subgroup of 51 participants (65%) who adhered to the study protocol for 4 years.[37] Assessments included static perimetry, ETDRS best-corrected VA, shape discrimination, final dark-adapted threshold, fundus image grade, and ellipsoid zone width (OCT metrics assessed at years 2 and 4). Only measures of VF sensitivity were associated significantly with DHA supplementation (e.g., the difference in annual rate of change was −0.47 dB [95% CI, −0.53 to −0.42 dB] per year). The perimetry measures were correlated significantly with erythrocyte DHA content ($r = -0.29$ to -0.55). Perimetry was performed with a size V target according to the 30-2 grid for all participants and a 30/60-2 program for participants with fields exceeding 30°. Notably, the treatment and control groups were imbalanced with respect to VF sensitivity at baseline, with the control group having a 44% greater mean total sensitivity (12.5 dB control group vs. 8.7 dB DHA group). Baseline sensitivity may contribute to a faster rate of decline in the control group because of floor effects and given the nonlinear VF decline dynamics that can be observed in RP.[38] Additionally, the analysis was not corrected for multiple comparisons.

A level II post hoc observational study[39] evaluated the functional impact of dietary omega-3 fatty acid intake among an aggregate group of 357 participants with RP from 3 separate clinical trials conducted between 1984 and 2008.[6,32,40] Estimates of dietary omega-3 fatty acid (primarily DHA) intake were obtained from food frequency questionnaires administered during each trial. The authors found that high dietary omega-3 fatty acid (≥ 0.2 g/day) intake was associated with a statistically significant reduction in rate of VA decline (−0.59 letter/year [high omega-3 intake] vs. −1.00 letter/year [low omega-3 intake]; $P = 0.001$), but no significant impact on photopic flicker electroretinography amplitudes (9.8% [high omega-3 intake] vs. 9.6% [low omega-3 intake]). This post hoc study of aggregated observational data has important limitations. First, the difference in VA loss between the two groups was approximately 0.4 letters/year, which is unlikely to be a clinically meaningful finding. Additionally, VA is not a typical endpoint in studies of RP; indeed, the same authors did not choose VA as a primary endpoint in any of the 3 clinical trials used in this study. No accounting for the presence of cystoid macular edema was made, one of the more common causes of VA loss in RP. Also, high potential exists for residual confounding among these groups with differing dietary habits.

Lutein

Lutein is a dietary carotenoid that is highly concentrated in the central macula. It is believed to protect the retina from photodamage by filtering blue light, serving as an antioxidant, or both.[41] Along with other antioxidants, it is part of the Age-Related Eye Disease Study 2 dietary supplement for individuals with age-related macular degeneration. One level I, one level II, and one level III study were identified that evaluated the impact of lutein supplementation in RP.

A 2010 level I randomized controlled trial evaluated the role of lutein in adults with RP.[40] This 4-year study randomized 240 participants 1:1 to 12 mg lutein plus 15 000 IU vitamin A daily versus placebo plus 15 000 IU vitamin A daily. The primary endpoint was the total point score using

an HVF 30-2 testing grid (size V stimulus), and prespecified secondary outcomes included 60-4 total point score, summed 30-2 and 60-4 total point score, photopic 30-Hz flicker electroretinography response amplitude, and ETDRS VA. No treatment effect was seen for the primary outcome among the 215 participants with measurable field sensitivities over 4 years of follow-up, with mean annual sensitivity losses of 49.6 dB/year (lutein plus vitamin A) and 51.5 dB/year (control plus vitamin A; $P = 0.66$), yielding a mean difference of −1.9 dB/year (95% CI, −10.7 to 6.9 dB/year). Among secondary outcomes, a statistically significant reduction in rate of HVF 60-4 sensitivity decline was found in the treatment arm (26.6 dB/year in the lutein arm vs. 34.1 dB/year in the control arm [$P = 0.05$], yielding a mean difference of −7.5 dB/year [95% CI, −16.0 to 1.0 dB/year]), and no treatment effect was observed with electroretinography or VA outcomes. The treatment effect on HVF 60-4 sensitivity was significantly greater among those with the highest serum lutein and highest increase in macular pigment optical density. No safety concerns were observed, although 2 participants in the treatment arm were required to withdraw because of abnormal liver function.

This was a well-designed study, yet some notes of caution should be observed in the interpretation of the secondary perimetry endpoints. The HVF 60-4 grid tests the midperipheral field and is challenging for patients with RP because of floor effects. The authors excluded all participants with a total point score at any visit of 0, resulting in inclusion of only 163 of the original 240 participants. Among this subgroup, the mean baseline total point scores of 360 dB and 393 dB for the treatment and control arms, respectively, seem imbalanced and are far less than normal (approximately 1300 dB using a smaller size III stimulus in healthy people).[42] Perhaps the 33-dB difference in baseline scores contributed to the differential rates of decline between the two study arms, which amounted to an approximate 30-dB total difference over the entirety of the 4-year study. Furthermore, the clinical significance of a 30-dB difference between study arms summed across the entire 60-point testing grid over 4 years is questionable. Finally, the authors did not adjust the analyses for multiple comparisons.

A 2006 level II trial randomized 45 participants to a placebo-then-lutein group or a lutein-then-placebo group, with crossover at 24 weeks and total follow-up of 48 weeks.[43] The primary endpoint was VA. Conventional outcomes including VA were reported in abstract form but were not published in a full-length manuscript and thus were not eligible for inclusion in this assessment. The authors published a full manuscript on a set of secondary outcomes composed of novel functional testing under varying illumination levels that was self-administered by the participants typically using a computer at home. Among these secondary outcomes, a small (0.018 [95% CI, 0.001−0.036]) but statistically significant effect on the log retinal area of VF was found ($P = 0.04$). The authors did not correct for multiple comparisons. It is unclear how these home-based outcomes compare with conventional perimetry assessments, which can be fraught with potential limitations even when performed by a trained examiner under rigorous testing conditions in a clinical research laboratory. Additionally, the study was small with participant attrition, and a per-protocol analysis (n = 34 [76%]) was performed.

In 2000, the same group published findings from a level III pilot uncontrolled study of 20 unmasked participants receiving lutein.[44] The primary outcomes, measured at 26 weeks, were self-reported VA and VF metrics measured at home. The analysis excluded 4 participants (20%) because of noncompliance and low baseline VA. The authors reported statistically significant improvements for high luminance VA (mean, approximately 8 ETDRS letters) and central VF (mean, approximately 0.067 log area). Similar limitations apply as with the prior study using home-based outcome measures.

Other Supplements

Vitamin E may serve an antioxidant role in the retina and is a component of the Age-Related Eye Disease Study supplements for age-related macular degeneration. A level II randomized controlled trial published in 1993 (see above) evaluated vitamin E supplementation (400 IU daily) along with high-dose vitamin A supplementation using a 2 × 2 factorial study design.[6] No statistically significant impact of high-dose vitamin E supplementation was found in the primary analysis, although the authors reported a significantly greater annual decline in the 30-Hz flicker amplitude with vitamin E supplementation among the subgroup of participants with high baseline electroretinography amplitudes (approximately 10.3% and 9.2% for the vitamin E and control groups, respectively; $P = 0.04$). Similar study limitations apply, as discussed above in "Vitamin A and Associated Compounds." Notably, even among this high-amplitude cohort, no significant finding resulted when data only to 4 years were evaluated, as originally intended.

A 2023 reanalysis of this study performed multiple additional analyses (see "Vitamin A and Associated Compounds") among the high-amplitude cohort.[12] These analyses did demonstrate a smaller but statistically significant deleterious effect of vitamin E supplementation on 30-Hz flicker amplitudes.

A level II 2019 randomized controlled trial evaluated oral supplementation with *Lycium barbarum* fruit extract on disease progression in RP.[45] *L. barbarum* fruit, or goji berry, is used in traditional Chinese medicine, and the authors proposed that its high zeaxanthin content and specific polysaccharides confer antioxidant properties that might be beneficial in RP. Notably, zeaxanthin is the primary xanthophyll pigment in the fovea. The study randomized 50 adult participants with RP in Hong Kong 1:1 to 5 g daily *L. barbarum* extract or lactose-based placebo for 12 months. The primary outcome measures were high-contrast and low-contrast corrected VA, measured at 6 and 12 months. Secondary outcome measures included macular center-point thickness on OCT imaging, scotopic and photopic electroretinography response amplitudes, and mean deviation on HVF 30-2 testing. The authors found a beneficial treatment effect at 12 months on high-contrast VA (mean difference, −0.13 logarithm of the minimum angle of resolution; $P = 0.001$) and on low-contrast VA (mean

difference, −0.22 logarithm of the minimum angle of resolution; $P = 0.001$), but not on electroretinography or HVF parameters. No notable safety concerns emerged.

A primary limitation of this study was the high rate of withdrawals (8 total, and 6 [24%] in the placebo arm) and the use of a per-protocol analysis (n = 42). The choice of the VA-based endpoint was unusual for a 1-year study, given that VA typically does not decline until later stages of RP and that the rate of decline can be quite slow and unpredictable. The treatment and control groups seemed to be imbalanced at baseline regarding VA and OCT endpoints, and the observed treatment effect largely was driven by the control group's relatively high 1-line reduction in VA over the 12-month study period. Further, no comment was made on cystoid macular edema or cataract, which can be important drivers of VA loss and retinal thickness change in RP.

A 2022 level II randomized controlled trial evaluated the antioxidant properties of a nutrient complex containing folic acid, vitamin B6, vitamin A, zinc, copper, selenium, lutein, and zeaxanthin among 31 patients with RP.[46] Visual outcomes were assessed at 24 months, with multifocal electroretinography amplitudes as the primary outcome. The authors observed a beneficial impact on multifocal P1 amplitudes, but not on the VF or OCT-based outcomes. Study limitations included the small sample size, high rate of withdrawals (6 total, and 5 [33%] in the treatment arm), lack of adjustment for multiple comparisons or for use of both eyes of each participant, and previously mentioned limitations of electroretinography-based outcomes.

A 2014 level III uncontrolled study evaluated the impact of 3 months of chlorogenic acid supplementation (60 mg daily) in 18 participants with RP.[47] Chlorogenic acid is a naturally occurring compound thought to exhibit antioxidant activity. The authors reported numerous outcomes based on comparing values before and after treatment and stated that multifocal electroretinography response amplitudes by ring represented the primary outcome. They identified a nominally significant beneficial treatment effect in mean ring 5 response amplitude, increasing from 7.2 μV (before treatment) to 8.3 μV (after treatment), yielding a mean difference 1.1 μV ($P = 0.02$), but no effect in other rings and no significant finding among numerous other outcome measures. The authors did not correct the analyses for multiple comparisons.

Study funding and author financial disclosures can be found in Table S2 (available at www.aaojournal.org).

Conclusions

The idea of dietary supplementation for RP represents a potentially attractive approach to reduce progression of this blinding disease with broad application across a variety of genotypes. However, at the time of this publication, no high-quality evidence firmly establishes efficacy of any form of dietary supplementation for individuals with RP. Numerous studies have highlighted data suggesting possible efficacy for supplements such as vitamin A, DHA, and lutein. In particular, ancillary outcomes of well-designed studies of lutein and DHA demonstrate a possible treatment effect that correlates with serum levels of the study supplement. Yet, in most cases, the positive findings derive from secondary outcome measures, analyses of subgroups of participants, post hoc analyses, or a combination thereof. Furthermore, among these findings, it is unclear whether the observed outcomes represent clinically meaningful effects. At most, these are hypothesis-generating findings that warrant further study. Finally, in some patients, dietary supplementation may pose health risks, as suggested by clinical trial data on vitamin E supplementation in RP, epidemiologic studies of high-dose vitamin A and β-carotene supplementation and systemic health, and studies raising concerns about the quality of products in the dietary supplement marketplace.

Future Research

The pioneering early trials of dietary supplementation in RP underscored challenges unique to the study of this rare and slowly progressive disease. Although the findings do not demonstrate clear efficacy, further study is warranted with large sample sizes, refined eligibility criteria, and clinically relevant primary endpoints. Future studies will benefit from the advent of novel endpoints to detect subtle changes in disease course. These include OCT-based structural outcomes such as ellipsoid zone parameters and individual retinal layer thicknesses and functional outcomes such as fundus-guided microperimetry, full-field stimulus testing, and multiluminance mobility testing. Disease-specific patient-reported outcome measures provide additional endpoints to assist in the clinical interpretation of changes observed by other investigations of visual function.

Notably, all studies evaluated in this assessment were performed at single clinical research centers. Recent years have seen a worldwide growth in IRD centers that are capable of conducting the rigorous testing required in studies of RP, and collaboration across centers has enabled large-scale studies to improve recruitment for RP and other IRDs.[48] Improved recruitment will allow studies to refine eligibility criteria and to identify study candidates most likely to exhibit measurable disease progression and to avoid floor and ceiling effects that may blunt the ability to detect treatment effects. Additionally, widespread access to high-quality genetic testing services will enable such studies to account for specific genotypes that may be more or less likely to benefit from the intervention. Finally, future studies should leverage the collaborative approach while striving for diversity and inclusivity to yield results that reflect the background genetic and phenotypic heterogeneity observed in RP.

Footnotes and Disclosures

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Abbreviations and Acronyms:
CI = confidence interval; **DHA** = docosahexaenoic acid; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FDA** = Food and Drug Administration; **HVF** = Humphrey visual field; **IRD** = inherited retinal disease; **RP** = retinitis pigmentosa; **VA** = visual acuity; **VF** = visual field.

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