The evidence for efficacy of omega-3 fatty acids in preventing or slowing the progression of retinitis pigmentosa: a systematic review

William G. Hodge,* MD, PhD, FRCSC; David Barnes,† MD; Howard M. Schachter,† PhD; Yi I. Pan,* MSc; Elizabeth C. Lowcock,* BScH; Li Zhang,† BSc; Margaret Sampson,† MLIS; Andra Morrison,† BSc; Khai Tran,† PhD; Maia Miguelez,† PhD; Gabriela Lewin,† MD

ABSTRACT • RÉSUMÉ

Background: Studies in preterm and term human infants have suggested that a dietary supply of omega-3 fatty acids is essential for optimal visual development. Several basic science studies support the hypothesis that omega-3 fatty acids may be useful therapeutic agents for pathologies of the retina and lens. As part of a systematic review of the effect of omega-3 fatty acids on eye health, the purpose of this study was to conduct a systematic review of the scientific–medical literature to appraise and synthesize the evidence for the effects of omega-3 fatty acids in preventing the development or progression of retinitis pigmentosa.

Methods: A comprehensive search was undertaken in MEDLINE, PREMEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Global Health, and Dissertation Abstracts. Unpublished literature was sought through manual searches of reference lists of included studies and key review articles and from the files of content experts. Searches were not restricted by language of publication, publication type, or study design. Eligibility criteria were applied to screen eligible studies on two levels. Data extraction and quality assessment were performed.

Results: Six studies published between 1995 and 2004 met eligibility criteria in investigating the question of the possible value of omega-3 fatty acids in slowing the progression of retinitis pigmentosa. Meta-analysis was not performed because there was not enough available information for formal quantitative analysis.

Interpretation: There are trends in improvement of some retinitis pigmentosa outcomes with omega-3 fatty acids in the higher quality studies. Clinical research is preliminary in this field, however. Accordingly, definitive answers will require significantly more observational and interventional clinical research.

Contexte : Les études menées chez des enfants nés prématurément ou à terme semblent indiquer que l'apport d'acides gras oméga-3 dans le régime alimentaire est essentiel au développement optimal de la vue. En science fondamentale, plusieurs études soutiennent l'hypothèse que les acides gras oméga-3 seraient d'utiles agents thérapeutiques pour les maladies de la rétine et du cristallin. Par une revue systématique des effets des acides gras oméga-3 sur la santé oculaire, cette étude se penche plus précisément sur la littérature en science médicale afin d'évaluer et de synthétiser les effets concrets des acides gras oméga-3 pour prévenir le développement ou la progression de la rétinite pigmentaire.

Méthodes : Une recherche exhaustive a été menée dans les bases de données MEDLINE, PREMEDLINE, EMBASE, Cochrane Controlled Trials Register, Global Health et les résumés de dissertations. On a fouillé manuellement dans la littérature non publiée les listes de références accompagnant les études et les principaux articles de revue, ainsi que dans les fichiers des spécialistes des contenus. La recherche ne s'est pas limitée à la langue ou au genre de publication ni aux plans d'étude. Des critères d'admissibilité ont été appliqués dans la sélection des études sur deux niveaux. On a extrait les données et évalué la qualité.

Résultats : Six études publiées entre 1995 et 2004 ont satisfait aux critères d'admissibilité visant à établir la valeur des acides gras oméga-3 pour ralentir la progression de la rétinite pigmentaire. L'on n'a pas fait de méta-analyse faute d'information suffisante disponible pour faire une analyse quantitative formelle.

From *the Department of Ophthalmology, Ottawa Hospital Eye Institute, University of Ottawa, Ottawa, Ont., and †the Chalmers Research Group, Children's Hospital of Eastern Ontario (CHEO) Research Institute, Ottawa, Ont.

Correspondence to: William G. Hodge, MD, PhD, University of Ottawa, Ottawa Hospital Eye Institute, 501 Smyth Road, Tower III, Ottawa ON K1H 8L6; fax (613) 739-6139; whodge@ottawahospital.on.ca.

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Interprétation : Dans les études de meilleure qualité, on discerne des tendances quant à l'amélioration de certains résultats de la rétinite pigmentaire grâce aux acides gras oméga-3. La recherche clinique en ce domaine est cependant préliminaire. En conséquence, il faudra beaucoup d'autres recherches cliniques sur le plan de l'observation et de l'intervention pour obtenir des réponses définitives.

The aim of this systematic review was to summarize the current evidence concerning the usefulness of omega-3 fatty acids in preventing the development or progression of retinitis pigmentosa (RP). In addition to informing the research community and the public on the effects of omega-3 fatty acids on RP, it was anticipated that the findings would be helpful in defining the agenda for future research.

Approximately 1.5 million people have RP worldwide,[1] and in Canada the estimated number of patients with RP is 12 000.[2] Retinitis pigmentosa is a group of inherited eye diseases that cause degeneration of the photoreceptor cells of the retina. In most forms of retinitis pigmentosa, the rod cells are the first to be affected. Early degeneration of rod cells results in night blindness. Symptoms are recognized most often in children, adolescents, and young adults. Few studies have attempted to quantify the rate of progression of RP. It has been reported that up to 60% of RP patients show decline in cone electroretinogram (ERG) amplitude over the course of 4 years and 64% show decline in rod ERG amplitude.[3] More specifically, the mean annual rates of decline of ocular functions in RP patients were reported as 1.8% for visual acuity, 2.6% for visual field area, and 8.7% for ERG amplitude.[4] Throughout their lifetime, as the disease progresses and more rod cells degenerate, patients lose their peripheral vision, and in advanced cases, their central vision.

The brain and eye are highly enriched with omega-3 fatty acids, which accumulate in these tissues during late fetal and early neonatal life.[5] Very high levels of the omega-3 fatty acid docosahexaenoic acid (DHA) are present in the retina, specifically in the disk membranes of the outer segments of photoreceptor cells. DHA accounts for over half the total fatty acyl groups present in the phospholipids of rod outer segment membranes, a proportion higher than that found in any other tissues.[6] Rod outer segments of the eye are unique specialized structures composed of stacks of membranous discs containing photosensitive proteins that detect and respond to light, thereby initiating the visual process. Rod outer segment membranes are constantly being renewed; however, the turnover of DHA from the outer segment disc to the retinal pigment epithelium is surprisingly slow. Furthermore, DHA appears to be maintained at a certain level in the retina despite reductions in dietary intake of omega-3 fatty acids.[7] This level of DHA may be maintained because of a possible protective role in increasing cellular phosphatidylserine; a decrease in DHA is observed to lead to a decrease in phosphatidylserine.[8] Therefore, DHA may play an important part in cell signaling and cell proliferation through the action of phosphatidylserine.

The high DHA content and its specific and consistent tissue distribution suggest that DHA has an important function in the retina.[9] Its specific role, although not well understood, may be related to its biophysical effects on the cell membrane. DHA influences the biophysical properties of membranes via its high polyunsaturation and may help to create a membrane that accommodates the dynamic behavior of rhodopsin during the photoreceptive process.[10–12] In addition, DHA may modulate both the activity of membrane-bound enzymes and receptors and the kinetics of membrane transport systems, as well as being a precursor for the synthesis of other biologically active molecules. A recent study suggests that DHA plays a role in modulating G-protein-coupled signaling pathways that are involved in visual transduction.[12] Previous studies have shown that RP patients have significantly reduced plasma DHA levels, suggesting the association between DHA deficiency and higher risk of RP.[13,14]

The lipid composition of cell membranes is affected by dietary factors, and the synthesis of phospholipids and their modification via polar head and acyl group turnover are metabolically regulated.[15] Thus, it is possible that under certain extrinsic (metabolic) and intrinsic (dietary) conditions a reduction in DHA occurs in the outer segment membranes that alters their physical and functional properties. A number of animal studies have shown that dietary deprivation of DHA results in abnormal ERGs and visual impairment that is accompanied by lower retinal levels of DHA-phospholipids.[16,17] Results from the Third National Health and Nutrition Examination Survey, 1988–94, indicated that an average North American consumes only 0.03 g of DHA per day.[18] Therefore, one practical consequence of studies in this area may ultimately be recommendation of daily intake levels for DHA.

Methods

Overall, the specific question addressed in this study

was "What is the evidence for efficacy of omega-3 fatty acids in preventing the development, or slowing the progression, of retinitis pigmentosa?" A technical expert panel was selected to help define this and other subsequent research questions, as well as to highlight key variables requiring consideration in the evidence synthesis, before the search began.

Study identification

The search strategy for this project was designed to be comprehensive and achieve the highest possible recall of relevant clinical studies. The electronic search strategy was developed by an information specialist in consultation with a clinical ophthalmologist and reviewed by a second information specialist. The eye search concept was combined with the core strategy of the omega-3 fatty acid search established in collaboration with the project librarians, biochemists, nutritionists, and clinicians. Consultation among these sources provided the biochemical names and abbreviations of omega-3 fatty acids, names of commercial omega-3 fatty acids products, and food sources of omega-3 fatty acids.

The following electronic databases were searched: MEDLINE (1966 to November week 2, 2003, and updated to February week 1, 2004), PREMEDLINE (updated to May 4, 2004), EMBASE (1980 to 2003 week 48, and updated to 2004 week 7), the Cochrane Library including the Cochrane Central Register of Controlled Trials (updated to 3rd quarter 2003), Global Health (1973 to December 2003) and Dissertation Abstracts (1980 to December 2004). All databases were searched via the Ovid interface except Global Health, which was searched through SilverPlatter. Searches were not restricted by language of publication, publication type, or study design, with the exception of the medical subject headings (MeSH) term "dietary fats," which was limited by study design to increase its specificity. A total of 721 bibliographic records were downloaded, duplicate records being identified and removed with citation management software (Reference Manager).

Reference lists of included studies, book chapters, and narrative or systematic reviews retrieved after having passed the first level of relevance screening were then manually searched to identify additional unique references. Through contact with content experts, attempts were made to identify both published and unpublished studies. A final set of 507 unique references was identified.

Eligibility criteria

Published and unpublished studies, written in any language, were eligible for inclusion. Studies had to specifically investigate foods or supplements known to contain omega-3 fatty acids of any type, from any source (e.g., fish, walnuts, seed oil), any serving size or dose, delivered in any fashion (e.g., capsules, liquids, diets rich in polyunsaturated fatty acids), and for any length of time. No restrictions were placed on the types or doses of pre- or on-study cointerventions (e.g., medication, omega-6 fatty acid intake, other dietary supplements).

Given the expectation that the relevant literature would be quite small, no restrictions were placed on the levels of evidence required for inclusion in the review. Nevertheless, for questions of intervention efficacy or effectiveness, it was assumed that evidence from randomized controlled trials (RCTs) would carry greater interpretative weight, since this research design is the gold standard method for investigating these questions.[19] Here, controlled studies of an observational nature were considered to carry greater interpretative weight than uncontrolled observational ones. Finally, greater interpretative weight was associated with results obtained from prospective designs than from retrospective designs.

Study selection process

The present review employed the Internet-based software system TrialStat (TrialStat Corporation, Ottawa, Ont.), housed on a secure Web site. Electronic yields of literature searches were posted to the system for review. Reviewers then submitted all their results of relevance screening, data appraisal, and data abstraction directly to the system. The software system automatically conducted an internal comparison of multiple reviewers' responses to screening questions to determine the eligibility or relevance of a bibliographic record or a full report. As well, the software captured responses to specific requests to abstract prespecified data (e.g., mean age of study participants; the assessment of a study's internal validity) from pertinent reports.

After we completed a calibration exercise that involved evaluating 5 sample reports using the same eligibility criteria, the reviewers' reports were independently assessed by 2 reviewers. The studies were screened at 2 levels: abstract only and full text. Reports were not masked, given the equivocal evidence regarding the benefits of this practice.[20] To be considered relevant at the second level of screening, all eligibility criteria had to be met. Disagreements arising at screening level 2 were resolved by requisite consensus and, if necessary, third party intervention. Excluded studies were noted as to the reason for their ineligibility and tabulated.

Data abstraction

Data abstracted included the characteristics of the

following parameters: type of report, type of study, population characteristics, exposure, cointerventions, outcomes, covariates, withdrawals and dropouts, and adverse events.

Study quality

For RCTs, we used the Jadad et al items[21] to assess the reporting of randomization, double blinding, and withdrawals and dropouts. Total scores ranged from 0 to 5, with a score less than 3 indicating low quality. The reporting of the concealment of a trial's allocation to treatment[22] received 3 grades (A, adequate; B, unclear; C, inadequate).

Assessing the quality of studies that had used designs other than RCTs was complicated by the dearth of validated instruments and the variety of such designs (e.g., nonrandomized controlled trials, uncontrolled studies). Nevertheless, a recent systematic review by Schulz et al identified a number of "best tools" for use with these designs.[22] Among them were a published instrument developed by Downs and Black[23] and an unpublished one derived by experts in Newcastle and Ottawa (NOS).[24] The former validated both design-specific and design-neutral items.

Where case–control and cohort studies were included in the review, the validated NOS was employed. Items applicable to other designs, such as non-RCTs, cross-sectional designs, cross-sectional surveys, and others, were taken from the Downs and Black instrument.

Qualitative and quantitative data synthesis

The results presented in this study are in the form of an organized, qualitative, and systematic review of the evidence gathered on the efficacy of omega-3 fatty acids in preventing or slowing RP. Given the paucity of relevant studies addressing this question, as well as the variability in research designs, definitions of study populations, exposures and interventions, and clinical outcomes employed to investigate it, meta-analysis of the evidence was deemed impossible or inappropriate.

RESULTS

Of the 507 records entered into the initial screening for relevance of the abstracts, 395 were excluded. Reflecting the specific eligibility criteria, the reasons for exclusion were (a) not a first publication of empirical evidence (e.g., a review; n = 93), (b) not involving human participants (n = 206), (c) no focus on omega-3 fatty acids (i.e., no intervention or exposure; n = 80), and (d) not related to predefined eye-health outcomes (n = 16). All reports that passed this level of screening were then retrieved and subjected to a more detailed relevance assessment. This second full-text screening excluded 96 reports for the same 4 reasons: (a) not a first publication of empirical evidence (n = 39), (b) not involving human participants (n = 8), (c) no focus on omega-3 fatty acids (n = 39), and (d) not related to predefined eye-health outcomes (n = 10). In the end, 16 articles were retained that were relevant to the effect of omega-3 fatty acids on eye health, but only 4 articles answered the question posed by this study. Two additional relevant articles published in September 2004 were subsequently identified and included in our review.

Overview

Table 1 summarizes 3 RCTs. Hoffman et al[25] conducted a 4-year RCT among male patients (mean age 16 y, range 4–38 y) with X-linked retinitis pigmentosa (XLRP), comparing 400 mg/d DHA (n = 23) with an identical-looking and -tasting gelatine placebo capsule (n = 21) containing 400 mg/d corn–soy oil triglyceride. Hypothesizing that low levels of DHA in XLRP might influence retinal function, they aimed to elevate red blood cell (RBC) DHA concentrations and to determine the effects of DHA supplementation on the progression of XLRP. Patients were primarily recruited from an RP registry in the southwestern part of the United States. The primary outcome was cone ERG response to a 31 Hz flicker stimulus. Secondary ocular outcomes included rod ERG response, Humphrey field analyzer (HFA) visual field, fundus photography, visual acuity, dark adaptation, responses to a visual activity questionnaire, and a patient opinion survey. Covariates assessed were age, race, body weight, and gene mutation. Safety outcomes (i.e., adverse events) were complemented by data from analyses of serum samples for fatty acid content, antioxidants, total antioxidant capacity, platelet aggregation, alanine aminotransferase activity, and lipoprotein-lipid profiles. Outcomes were assessed every 6 months. Descriptions in the report did not reveal inappropriate methods of handling or analyzing lipid samples.

Berson et al[26] conducted an RCT (Study 1) on 208 RP patients who were randomly assigned to receive either 1200 mg/d DHA (n = 105, mean age 37.8 y) or a placebo (n = 103, mean age 36.0 y) in addition to a standard 15 000 IU/d vitamin A supplement. On the basis of findings that some patients with RP display decreased levels of RBC DHA compared with that of control subjects without RP, the authors were examining the question of whether a DHA supplement could slow the course of RP in adult patients who were also receiv-

Table 1—Summary of 3 randomized controlled trials on the effect of omega-3 fatty acids on progression of retinitis pigmentosa

Author, location	Year	Duration, design	Treatment		Internal validity
			Intervention	Placebo	
Hoffman et al[25] US	2004	4 y parallel RCT	400 mg/d DHA (*n* = 23)	400 mg/d corn–soy oil triglyceride (*n* = 21)	Jadad total: 4 [Grade: A]; Schulz: Adequate
Berson et al[26] US	2004	4 y parallel RCT, (Study 1)	1 200 mg/d DHA 15 000 IU/d retinyl palmitate (*n* = 105)	Control fatty acid 15 000 IU/d retinyl palmitate (*n* = 103)	Jadad total: 5 [Grade: A]; Schulz: Unclear
Berson et al[27] US	2004	4 y parallel RCT, (Study 2)	1 200 mg/d DHA 15 000 IU/d retinyl palmitate (*n* = 105)	Control fatty acid 15 000 IU/d retinyl palmitate (*n* = 103)	Jadad total: 5 [Grade: A]; Schulz: Unclear

Note: RCT = randomized controlled trial; DHA = omega-3 fatty acid docosahexaenoic acid; Jadad total = Jadad total quality score (/5): reporting of randomization, blinding, withdrawals, and dropouts;[21] Schulz = reporting of adequacy of allocation concealment (adequate, unclear, inadequate).[22]

ing vitamin A. Approximately 70% of the patients in both the intervention and control group were already on vitamin A supplement treatment before enrolment of the study. Berson et al[27] then performed a subgroup analysis (Study 2) to determine whether DHA would slow the course of progression of RP in this subset of patients. Patients were assessed annually over 4 years.[26,27] The primary outcome measure was the total score of HFA 30-2 program field. Annual rates of decline were estimated by HFA 30-2 program field, HFA total field, 30-Hz ERG amplitude, and Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity. Secondary outcomes included serum levels of triglyceride, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. During the 4-year follow-up, no adverse event or toxic effect relating to DHA supplement intake was reported.

Dagnelie et al[28] (Table 2) performed a comparative before–after study over 6 months involving 20 volunteers, recruited over the internet from an RP list, who were then divided into 2 groups. One group (*n* = 10) received lutein alone (40 mg/d for 9 weeks, 20 mg/d thereafter), while the second group (*n* = 10) received lutein (40 mg/d for 9 weeks, 20 mg/d thereafter) plus 500 mg/d DHA, vitamin B complex (dose not reported), and 600 mg/d digestive enzymes. The purpose of the study was to examine the impact of lutein supplementation. Ten patients were not discouraged from continuing additional prestudy supplements while on-study (e.g., vitamin A palmitate and (or) beta carotene), thereby compounding the failure to give a placebo to the lutein-alone group to control for the supplementation received by the other group. Four patients ultimately had insufficient data for analysis. Only 13 of the remaining 16 patients were specifically identified with RP; the other 3 patients (*n* = 2 in lutein-alone group) exhibited other retinal degenerations outside the focus of the present review. The primary outcomes were self-tested visual acuity and central visual acuity evaluated weekly for 14 weeks and biweekly thereafter. Age, sex, eye color, and RP disease type were also recorded.

Hoffman et al[29] performed 2 small studies of omega-3 fatty acid supplementation in patients with autosomal dominant RP (patients in the second study had RP attributable to rhodopsin mutations), where visual function was a secondary outcome. Although controls were included in each trial, they received the same supplementation as did the 2 patient groups. Moreover, the results of the controls were not provided. For the purposes of the present review, it was thus decided to examine only the data from the RP patients, effectively making each of these designs a noncomparative before–after study. Several ocular parameters were measured in each study, including ERG, visual acuity, and visual fields, but only ERG results were reported. Covariates were not assessed in either study. In both studies, participants' diets were first modified to reduce possible on-study variability in background intake of omega-3 fatty acid.[29] Then, in Study 1, 3 patients with autosomal dominant RP were given a 3 g/d oral dose of a purified fish-oil concentrate (0.7 g/d DHA and 1.3 g/d eicosapentaenoic acid [EPA]) for 6 weeks. In Study 2, 3 patients with autosomal dominant RP were given a purified preparation of EPA ethyl ester (99.4% purity, dose not reported) for 3 weeks. In each study, 0.2 mg/g tert-butyl hydroquinone and 2 mg/g tocopherols were added as antioxidants to maintain the exposure's freshness. Whether capsules were used to deliver the

Table 2—Quasi-experimental studies on the effect of omega-3 fatty acids on progression of retinitis pigmentosa

Author, location	Year	Duration, design	Treatment		Internal validity
			Intervention	Placebo	
Dagnelie et al[28] US, Canada, & 7 other countries	2000	6 mo comparative before–after study	Lutein (40 mg/d for 9 wk, 20 mg/d thereafter) + 500 mg/d DHA + vitamin B complex (dose not reported) + 600 mg/d digestive enzymes (n = 10)	Lutein alone (40 mg/d for 9 wk, 20 mg/d thereafter) (n = 10)	Total quality: 2 [Grade: C]
Hoffman et al[29] US	1995	6 wk noncomparative before–after study 1	3 g/d purified fish oil (0.7 g/d DHA + 1.3 g/d EPA) (n = 3)		Total quality: 4 [Grade: C]
Hoffman et al[29] US	1995	3 wk noncomparative before–after study 2	EPA ethyl ester (dose not reported) (n = 3)		Total quality: 3 [Grade: C]

Note: DHA = omega-3 fatty acid docosahexaenoic acid; EPA = eicosapentaenoic acid; internal validity = Jadad total quality score (/5): reporting of randomization, blinding, withdrawals, and dropouts.[21]

exposures was unclear. A key focus of each study was the impact of supplementation on RBC fatty acid contents.

Qualitative synthesis of key study characteristics

Study

The inclusion and exclusion criteria in Hoffman et al's RCT[25] were well documented, and randomization was discussed in detail. Masking was implied but not explicitly detailed. Compliance was measured as RBC DHA content. A sample size calculation and descriptions of losses to follow-up were provided. An intention-to-treat analysis was undertaken. No details regarding interim analysis were provided.

Berson et al's RCT[26,27] was well designed and executed. Specific inclusion and exclusion criteria in 3 areas (ocular; dietary; and medical and other) were given. Randomization and assignment allocation were both clearly described, and masking was adequately explained. Compliance in both the experimental and control group was high, as confirmed by the level of RBC phosphatidylethanolamine (PE) DHA. Sample size calculation was explained and losses to follow-up were also described but not accorded to groups. This was not an intention-to-treat analysis; however, there were only 4 withdrawals, and a sensitivity analysis was done on all 221 randomized patients after they used multiple imputation methods to account for missing data.

Dagnelie et al's[28] eligibility criteria were poorly detailed. Their funding source was not provided. These investigators provided few details regarding the selection criteria. Selection criteria for Hoffman et al's[29] 2 small studies were sparse.

Population

Male patients with XLRP in Hoffman et al's RCT[25] were recruited from the Southwest Eye Registry of the Retina Foundation and from clinical centers supported by the Foundation Fighting Blindness. Eligibility criteria included a retina specialist's diagnosis of RP, a family history consistent with X-linked inheritance, a large-amplitude cone response, and a baseline diet that did not purposely include large amounts of omega-3 fatty acids. Fifty-two individuals were assessed for eligibility and 44 were randomized.

Berson et al[26,27] examined 456 patients across the United States and recruited 221 eligible patients with RP from 221 different families. Six percent of these patients were members of ethnic minorities, and 11% reported partial hearing loss; 50% of the experimental group and 64% of the control group had cataracts in at least one eye at baseline check-up.

The source population in the Dagnelie et al[28] study was not clearly documented. The sample came from an internet RP list, yet additional details regarding recruitment were not provided. Of the 30 listed patients who initially showed interest, 20 decided to enroll in the study. Of these 20, 4 did not provide sufficient data and hence the final analyzed sample included 16 participants. The patients came from 9 different countries,

with 60% from the United States (n = 7) and Canada (n = 5). Age and sex were noted in the study. The mode of inheritance of RP was varied in these patients.

In Hoffman et al's[29] 2 noncomparative before–after studies, the source populations were not described. In the fish-oil study (Study 1), two thirds of the patients were male, with a mean age of 31.7 years. In the EPA study (Study 2), two thirds of the patients were female, with a mean age of 29.3 years, and they had documented mutations in the rhodopsin gene.

Intervention and exposure

Hoffman et al's RCT report[25] clearly defined the intervention received by both study groups and its method of delivery via capsules. A total fat content of 400 mg was provided daily for both study groups. Those patients taking the DHA content essentially received about 10 mg of DHA per kilogram of body weight per day. The DHA-enriched oil came from a single-cell algal source and was provided as a highly purified triacylglycerol. The investigators provided descriptions concerning the purity of their omega-3 fatty acid contents, and their source company (Martek Biosciences Corporation, Columbia, Md.).

The intervention employed by Berson et al[26,27] was giving patients 1200 mg/d of DHA in the form of capsules (Martek). The controls received 1200 mg/d of a mixture of soybean and corn oils (Martek). The 15 000 IU/d vitamin A supplement that was available to all study patients was prepared by Akorn, Inc., Buffalo Grove, Ill. The composition of all capsules was described in detail.

Dagnelie et al[28] mentioned the names of manufacturers of their supplements, yet no purity data were supplied. These same investigators did not report compliance data. The purity of Hoffman et al's[29] noncomparative before–after Study 2 exposure was identified, as was the source of their omega-3 fatty acid contents for both studies (Fish Oils Test Materials Program, National Institutes of Health and the National Oceanic and Atmospheric Administration, Charleston, S.C.).

Outcome

Visual outcomes were recorded annually and the total duration of the Hoffman et al RCT[25] was 4 years. Their primary outcome was cone ERG response amplitudes to a 31Hz flicker stimulus with the pupils maximally dilated. Rod response was assessed as a secondary outcome. An HFA visual field 30-2 was also performed and the mean defect was the specific outcome used. Fundus photographs were taken according to the ETDRS protocol, and grading was completed. A visual activity questionnaire was given to all patients. A patient survey of the perceived benefit of the intervention was included. Additional outcomes included specific biological safety data: total fatty acid content, and their relative ratios, vitamin A and E levels (μg/dL), total antioxidant capacity in synthetic vitamin E equivalents, platelet aggregation (impedance units), alanine aminotransferase activity (U/L) and lipoprotein-lipid profiles (mg/dL). Patients were also requested to report all adverse events.

Berson et al's RCT[26,27] followed patients for 4 years; outcomes were measured annually. Primary outcome measures included the measurement of static perimetric sensitivities with the 30-2 program HFA (size V). Full-field 30 Hz ERG amplitude was used as the secondary outcome measure, since the area of visual field is correlated to ERG amplitude, and the 30-Hz ERG amplitude was also measured at screening and baseline check-up. At each study visit, medical history, dietary intake, ophthalmologic findings, serum retinol and retinyl ester levels, and plasma DHA level were measured. RBC PE DHA level was measured at baseline, 1 year, and the final study visit at 4 years. Patients were required to report any adverse events or changes in ophthalmic condition.

In the Dagnelie et al[28] study, the investigators created 6 visual acuity charts in the form of Microsoft Word files. Patients were instructed to use the 6 charts in rotation on their monitor at arm's length and not to change the working distance. Patients entered the number of letters seen in this binocular test on a weekly report form. For central visual field testing, the patients had to create their own field via instructions given to them. The field area seen was recorded by the patient and submitted via the internet. Participants submitted data each week for 26 weeks and included subjective data on glare, dark and light adaptation, night vision, color vision, depth perception, peripheral vision, and adverse event data with respect to allergy or irritation in the eyes. Each subjective answer was binary, but a more detailed questionnaire, which used a nonvalidated scale, was completed at the end of the study.

In the 2 Hoffman et al[29] noncomparative before–after studies, best-corrected visual acuity was measured with Bailey-Lovie eye charts. The better eye was then used for the rest of the testing. Kinetic visual fields were obtained with Goldmann IV-4e spot sizes.

Study quality

Although the Hoffman et al[25] (only males were enrolled) and Berson et al[26,27] RCTs both received a

total quality grade of A, the 3 quasi-experimental studies by Dagnelie et al[28] and Hoffman et al[29] each attained a total quality grade of C.

Qualitative synthesis of study results

By the fourth year of Hoffman et al's RCT,[25] the average loss of cone function in the DHA supplementation group was 25% lower than that observed in the control group, but this difference was not statistically significant. Given that 5 patients were deemed noncompliant on the basis of RBC levels of DHA, secondary analyses were performed to explore the relationship between RBC DHA level and ERG progression. None of the results achieved a level of statistical significance, however. Rod ERG loss was 48% lower in the DHA group than in the control group, yet this difference was also not statistically significant. The rod and cone loss showed effect modification by age. Specifically, the rod functional loss was significantly reduced in the prepuberty group supplemented with DHA compared with placebo ($p = 0.04$), and the cone functional loss was significantly reduced in the postpuberty group supplemented with DHA compared with placebo ($p = 0.038$).

Visual field, acuity, and dark adaptation outcomes did not differ between the groups.[25] Significantly less progression of RP in the DHA group than in the placebo ($p = 0.04$) was documented by fundus photographs. Visual activity questionnaire results were not different in the 2 groups, but significantly more patients receiving DHA supplementation believed their treatment had benefited them than did placebo patients. Stratification for genetic mutation status did not yield between-group differences.[25] There were no between-group differences in the results relating to the biological safety assessment.

Over the 4 years of follow-up, Berson et al (Study 1)[26] observed a trend in both the intervention and control groups of decreasing central field sensitivity (dB), total field sensitivity (dB), 30 Hz ERG amplitude, and ETDRS visual acuity. The analysis of mean changes from baseline to year 4, however, did not show any statistically significant difference between the 2 groups (p values ranged from 0.64 to 0.88 for the 4 parameters). As for serum levels of fatty acids, the control group had significantly higher serum triglyceride levels than the intervention group ($p < 0.001$), but also significantly lower levels of serum low-density lipoprotein cholesterol ($p < 0.001$).

On the other hand, in their subgroup analysis (Study 2), Berson et al[27] discovered that DHA supplementation significantly lowered the annual rate of decline in ocular function in patients who had not received vitamin A supplement before study enrolment. It was shown that the rate of decline in HFA 30-2 field, HFA total field, and 30 Hz ERG were all significantly slower in the intervention group ($p = 0.002$, 0.001, and 0.02, respectively) of the subgroup that was not on vitamin A before the study. The authors also performed a trend analysis on the entire study cohort using annual decline in total visual field sensitivity as a function of RBC PE DHA level. The results indicated that patients who demonstrated lower RBC PE DHA levels showed faster decline in visual field sensitivity than those with higher RBC PE DHA levels ($p = 0.05$); this trend was even more obviously demonstrated in the subgroup of patient not on vitamin A before the study ($p = 0.003$, from baseline to year 2). In the subgroup of control patients who were already on vitamin A supplement before enrolment, having a dietary omega-3 fatty acid intake of ≥0.20 g/d significantly decreased the rate of annual decline for the central visual field sensitivity ($p = 0.02$) and total visual field sensitivity ($p = 0.05$). There was no statistically significant difference between the subgroups with respect to visual acuity.

In the Dagnelie et al[28] study, there were statistically significant improvements in visual acuity and kinetic visual fields for the 16 participants ($p = 0.05$). Analysis by supplement type (lutein alone vs. lutein plus omega-3 fatty acids plus vitamin B and enzymes) failed to pinpoint a significant difference for either outcome, but there was a trend for improvement in both outcomes for the lutein-alone group. Either way, given the study design it was impossible to isolate the specific impact of the omega-3 fatty acids on clinical outcomes. Dagnelie et al's study report did not present outcome data organized to allow a meaningful investigation of only those data from patients with RP.[28] In Hoffman et al's[29] 2 noncomparative before–after studies, the ERG results showed no statistically significant before–after changes.

Impact of covariates and confounders

In Hoffman et al's RCT,[25] age, race, and body weight were recorded. A gene mutation analysis was also performed, distinguishing between the *RPGR* mutation and the *RP24* mutation. Dagnelie et al[28] measured age, race, country of origin, baseline supplementation, and type of RP. There was a paucity of detail, however, concerning the regression models designed to assess the influence of these possible effect modifiers. In Hoffman et al's[29] 2 noncomparative before–after studies' reports, age, sex, and rhodopsin gene mutation data were provided. Nonetheless, given the extremely small sample sizes within each study, meaningful effect modification analysis could not be performed.

Interpretation

The possible impact of the intake of omega-3 fatty acids on RP was examined in 6 studies,[25–29] 2 of which were described in a report published by Hoffman et al.[29] Study designs included 3 RCTs[25–27] and 3 quasi-experimental designs.[28,29]

The 6 studies examining whether the intake of omega-3 fatty acids slows the progression of RP did not provide a conclusive answer to this question.[25,28,29] The 3 RCTs constituted the most rigorous studies and revealed conflicting results.[25–27] In the Hoffman et al study,[25] rod and cone functional loss showed effect modification by age, with rod loss significantly reduced in the prepuberty group supplemented with DHA compared with placebo, and cone loss significantly reduced in the postpuberty group supplemented with DHA compared with placebo. The observation that certain analyses failed to reveal statistically significant between-group differences could be explained by this having been an underpowered trial.[25] In the Berson studies,[26–27] DHA supplementation did not produce a significant difference in the overall sample, but it was beneficial in those who had not previously received supplemental vitamin A.

By virtue of its research design, which did not permit the isolation of the specific impact of omega-3 fatty acids on slowing the progression of RP, Dagnelie et al's[28] internet-based comparative before–after study cannot be used to meaningfully address this question. In Hoffman et al's[29] 2 small noncomparative before–after studies of short duration, ERG results did not reveal statistically significant changes following supplementation.

From our systematic review of the results of these published studies, we conclude that there are some suggestive trends that omega-3 fatty acid supplementation may benefit RP patients, but the evidence as it now stands has not proven significant benefit. Further observational and interventional research is needed to definitively answer this question.

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The full reports of omega-3 fatty acids on human health are available from the Agency for Healthcare Research and Quality, Rockville, Md.

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