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Effects of Omega-3 Fatty Acids on Eye Health

Summary

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Introduction

The purpose of this study was to conduct a systematic review of the scientific-medical literature to identify, appraise, and synthesize the human evidence for the effects of omega-3 fatty acids on eye health. The review was requested and funded by the Office of Dietary Supplements, National Institutes of Health. It was undertaken as part of a consortium involving three Evidence-based Practice Centers (EPCs), which investigated the value of omega-3 fatty acid supplementation across eleven health/disease areas. The three EPCs are Southern California-RAND, Tufts-New England Medical Center, and the University of Ottawa. To ensure consistency of approach, the three EPCs collaborated on selected methodologic elements, including literature search strategies, rating of evidence, and data table design.

Visual health is a broad topic, yet we focused on eye health conditions that have a large public health impact in North America. Impact was defined in various ways. Our definition encompassed conditions that either demonstrate high prevalence (e.g., diabetic retinopathy, age-related macular degeneration [ARMD], and retinal vascular occlusions), produce many potential years of vision loss in that they affect the young (e.g., retinitis pigmentosa [RP]), or constitute a challenge to health services in no small part because they are costly to treat (e.g., cataracts).

The brain and eye are highly enriched with omega-3 fatty acids, which accumulate in these tissues during late fetal and early neonatal life.[1] Very high levels of 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 is found in any other tissues.[2] Its specific role, however, is not well understood. The role of DHA 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.[3-5] In addition, DHA may modulate 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 number of studies in preterm and term human infants have suggested that a dietary supply of omega-3 fatty acids may be essential for optimal visual development.[6-8] Finally, animal data suggest that retinal degeneration in rats might be prevented by dietary intake of DHA,[9] and DHA administered before ischemia may

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reduce pressure-induced retinal damage in monkeys.[10] It is against this backdrop that the key questions were investigated. Our project's overarching goal was to systematically review the human evidence to help develop a research agenda.

Key Questions

The key questions are organized by type of eye disease or visual impairment.

Degenerative diseases of the retina—macular degeneration:

- What is the evidence for efficacy of omega-3 fatty acids in preventing ARMD and slowing the progression of ARMD?
- What is the evidence that omega-3 fatty acids decrease the rate of progression to advanced forms of macular degeneration in all patients, diabetics, and patients with cataracts?
- What is the evidence that omega-3 fatty acids decrease the rate of progression of advanced forms of macular degeneration in all patients, diabetics, and patients with cataracts?

Degenerative diseases of the retina—retinitis pigmentosa:

- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of RP (i.e., an inherited retinal dystrophy)?

Vascular diseases of the retina—retinal vein or retinal artery occlusions:

- What is the evidence for efficacy of omega-3 fatty acids in preventing retinal vein occlusion and retinal artery occlusion?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of retinal vein occlusion and retinal artery occlusion?

Vascular diseases of the retina in diabetics:

- What is the evidence for efficacy of omega-3 fatty acids in preventing proliferative retinopathy in diabetics?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of proliferative retinopathy in diabetics?
- What is the evidence for efficacy of omega-3 fatty acids in preventing clinically significant macular edema in patients with diabetic retinopathy?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of clinically significant macular edema in patients with diabetic retinopathy?

Cataracts:

- What is the evidence for efficacy of omega-3 fatty acids in preventing age-related cataracts?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the rate of progression of age-related cataracts in all patients, diabetics, and patients with ARMD?
- What is the evidence that omega-3 fatty acids decrease the rate of cataract surgery in aging populations?

Adverse events:

- What is the evidence for the risk of short- and long-term adverse events related to the intake of omega-3 fatty acids?

Methods

A Technical Expert Panel was convened to provide advisory support to the project, including refining the questions and highlighting key variables requiring consideration in the evidence synthesis.

Study Identification

Several electronic databases were searched: MEDLINE® (1966–November Week 2 2003 and updated to February Week 1 2004), PreMEDLINE® (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 (3rd Quarter 2003), and CAB Health (1973–Dec 2003). Searches were not restricted by language of publication, publication type, or study design, except with respect to the MeSH® term "dietary fats," which was limited by study design to increase its specificity. Search elements included: scientific terms, with acronyms, as well as generic and trade names relating to the exposure and its sources (e.g., eicosapentaenoic acid (EPA); omega-3 fatty acids; MaxEPA®); and, relevant population terms (e.g., macular degeneration). Additional published or unpublished literature was sought through manual searches of reference lists of included studies and key review articles, and from the files of content experts. A

final set of 507 unique references was identified and posted to an Internet-based software system for review.

Studies were considered relevant if they described live human populations of any age, investigated the use of any source, type, dose, or method to deliver omega-3 fatty acids as primary or secondary prevention for any of the above-noted eye health conditions in any of the populations or subpopulations of interest (e.g., diabetics), and investigated at least one pertinent clinical outcome (e.g., prevalence, incidence; change in clinical status; need for cataract surgery). No restrictions were placed on the requisite levels of evidence (i.e., study designs) given the expected dearth of studies. As markers of omega-3 fatty acid metabolism, the following fatty acid compositions or concentrations, from any source (e.g., red blood cell membranes, plasma phospholipids), were considered relevant: EPA, DHA, arachidonic acid (AA)/EPA, AA/DHA, and AA/EPA+DHA.

Two initial levels of screening for relevance, and two reviewers per level, were employed (directed at bibliographic records, then full articles). Calibration exercises preceded each step of the screening process. Excluded studies were noted as to the reason for their ineligibility using a modified QUOROM format.[11] Disagreements were resolved by forced consensus and, if necessary, third party intervention.

Data Abstraction

Following a calibration exercise, two reviewers independently abstracted the contents of included studies using an electronic Data Abstraction form developed especially for this review. A third reviewer then verified the data. Data abstracted included characteristics of the following:

- Report (e.g., publication status, language of publication, year of publication).
- Study (e.g., sample size, research design, number of study arms/groups).
- Population (e.g., age; diagnosis, including severity, duration, and comorbidity).
- Intervention/exposure (e.g., omega-3 fatty acid types, sources, doses, and intervention/exposure length), and comparator(s).
- Cointerventions (e.g., concurrent treatments/medications, omega-6 fatty acid use).
- Withdrawals and dropouts, including reasons.
- Clinical outcomes.
- Fatty acid content of biomarkers.
- Adverse events (e.g., side effects).

Data Synthesis

A summary table provided a question-specific overview of included studies' relevant data presented in greater detail in evidence tables. A question-specific summary matrix situated each study in terms of its quality (i.e., internal validity) and applicability ratings (i.e., generalizability to the North American population). Question-specific qualitative syntheses of the evidence were derived. While no restrictions were placed on study designs, greater interpretative weight was given to prospective and controlled designs. Given the paucity of relevant studies addressing any given question, as well as the variability in the research designs, definitions of the study populations, exposures/interventions or clinical outcomes employed to investigate it, meta-analysis was deemed impossible or inappropriate with respect to each of the questions.

Results

Sixteen unique studies were identified, which addressed nine of the 23 questions posed by our project. Only two studies were randomized clinical trials (RCTs).[12,13] The vast majority of investigations employed either a before-after or observational study design. The paucity of interventional studies involving omega-3 fatty acids delivered as supplementation made it difficult to ascertain the rates or types of harm. The single, placebo-controlled RCT systematically reporting harm data revealed few minor, mainly gastrointestinal, effects associated with low-dose DHA supplementation.[13]

The most-frequently investigated question concerned the primary prevention of ARMD.[14-19] Designs included a single prospective cohort study,[16] two case-control studies,[14,15] one retrospective population-based cohort study,[19] and two single population cross-sectional studies.[17,18] There are sufficient between and within study conflicts (e.g., results of univariate vs. multivariate analyses) in the results to preclude drawing any inference that is conclusive with respect to the value of the intake of omega-3 fatty acids to prevent ARMD. If it can be assumed that the study designs likely best suited to address this question should be both controlled and prospective, none of the included studies would qualify. The only prospective study included a large sample and appropriately conducted multivariate analysis, and controlled for key confounders.[14] These investigators observed that the consumption of canned

tuna fish or more than four fish servings per week each played a protective role against ARMD. However, their results also indicated that several types of oily fish well known to have high concentrations of DHA and EPA (i.e., sardines, mackerel) failed to show a similar, protective effect. These discordant observations will require an explanation before anything conclusive can be asserted based on this study alone. Moreover, their study design did not *a priori* employ a separate, unexposed cohort as a control. The remaining studies cannot resolve the divergent primary prevention results described by this study, even though each of the former failed to demonstrate a statistically significant association between exposure and outcome.[14,15,17-19] Foremost among reasons is the use of research designs that constitute less than ideal strategies to investigate this question. These studies also varied in their definitions of the exposure, clinical outcome, and/or confounders, which together make it impossible to draw a definitive conclusion regarding the potential of the intake of omega-3 fatty acids to prevent the onset of either early or late ARMD.

The nature of the RCT design and the "cocktail-like" exposure employed by Scorolli et al. made it impossible to isolate the specific impact of omega-3 fatty acids on slowing the progression of ARMD.[12] A small sample size, the uncommonness and dubious clinical relevance of the visual recovery outcome, low study quality, and little or no applicability to the North American population suggest that there are, at present, no data with which to meaningfully address this research question.

Seddon et al.'s single prospective cohort study found that fish intake did not affect the progression to advanced ARMD overall, or in a high linoleic acid (LA) consumption group, but did protect against the progression to advanced ARMD in the low (below median consumption) LA consumption group.[20] This parallels what was observed exclusively via a significant test for trend in the Seddon et al. study described earlier with reference to its investigation of the influence of the intake of omega-3 fatty acids on preventing the onset of advanced ARMD.[15] However, the results from neither study can be used as yet to provide a conclusive answer to their respective research questions. Both require replication and a plausible explanation.

The four studies examining whether the intake of omega-3 fatty acids slows the progression of RP do not provide a conclusive answer to this question.[13,21,22] Hoffman et al.'s good quality RCT constituted the most rigorous test and revealed conflicting results.[13] That said, 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 post-puberty 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.[13]

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, results from Dagnelie et al.'s Internet-based comparative before-after study cannot be used to meaningfully address this question.[21] In Hoffman et al.'s two very small noncomparative before-after studies of short duration, electroretinogram results did not reveal statistically significant changes following supplementation.[22] Thus, until Hoffman et al.'s RCT[13] is replicated with a much larger sample size, little that is conclusive can be said about the potential value of the intake of omega-3 fatty acids in slowing the progression of RP.

Sorokin et al.'s noncomparative before-after study received a low study quality score and failed to resolve the questions of whether the intake of omega-3 fatty acids can slow the progression of either proliferative retinopathy or clinically significant macular edema in patients with diabetic retinopathy.[23] This study did not constitute the best test of either of these possibilities, however. The most relevant clinical outcome by North American standards entailed fundus assessments, yet few details were reported. Covariates were not measured, and the univariate analysis of the data was flawed. Thus, the results of this study are inconclusive with respect to these two possible benefits of the intake of omega-3 fatty acids in diabetic retinopathy.

Although both the Arnarsson et al.[24] and Cumming et al.[25] studies are well known population-based risk factor studies, in neither of them was the association between the intake of foods or oils containing omega-3 fatty acids and age-related cataract prevalence the primary question. That said, no statistically significant associations were observed. Cross-sectional designs constitute very limited evaluations of this question.

Suzuki et al.'s noncomparative before-after study did not assess cataract status as its clinical outcome, preferring instead to examine visual acuity.[26] Thus, with improvements in visual acuity unlikely to have been produced by reduced cataract formation, this study does not directly address the question of whether the intake of omega-3 fatty acids can slow the rate of progression of age-related cataracts.

A paucity of data prevented us from examining the possible influence on efficacy, association, or safety evidence of various covariates, which included both population (e.g., age at onset or diagnosis, smoking, alcohol consumption) and intervention/exposure factors (e.g., source, type, dose, and method to deliver omega-3 fatty acids; intake of omega-6 fatty acids).

Discussion

Based on the studies identified by this review, it is apparent that clinical research has only scratched the surface with respect to understanding the possible utility of the intake of omega-3 fatty acids as a primary or secondary prevention in eye health. Moreover, seen from the point of view of clinical research's typical, linear arc—which moves from basic science to observational research to RCTs, and culminating in the systematic review/meta-analysis of the observations obtained by these primary studies—there is a paucity of solid observational research with which to construct an experimental framework affording the meaningful conduct of RCTs. For example, there is little understanding of the exact sources, types, and doses of omega-3 fatty acids, or even the possible duration of their use, which might usefully serve as definitions of a prevention-centered "intervention" for any of the eye diseases/visual impairments examined in our review. Moreover, a single study reporting adverse event data likely does not permit laying to rest all possible concerns regarding the short- or long-term safety of such an intervention.

It is therefore our view that much more research will need to be conducted before anything conclusive can be asserted with respect to the effects of omega-3 fatty acids on eye health. It is also our understanding that sorting out the possible benefits of the intake of omega-3 fatty acids in eye health might profit from taking into consideration the impact of the concurrent intake of omega-6 fatty acids and, by definition, the omega-6/omega-3 fatty acid intake ratio. Finally, any notable causal or correlational relationships observed between the omega-6/omega-3 fatty acid intake ratio and the development or progression of eye disease/visual impairment may then be "explained" by future studies, which focus on observing patterns of omega-6/omega-3 fatty acid content in peripheral, or even brain, biomarkers.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center under Contract No. 290-02-0021. It is expected to be available in July 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 117, *Effects of Omega-3 Fatty Acids on Eye Health*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

Suggested Citation

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