Summary

Overview

This report was requested and funded by the Office of Dietary Supplements, National Institutes of Health. It is one of several reports focusing on the role of omega-3 fatty acids in the prevention or treatment of various diseases. Three Evidence-Based Practice Centers (EPCs) produced this series of reports: the Southern California EPC (SCEPC, based at RAND), the Tufts-New England Medical Center (NEMC) EPC, and the University of Ottawa EPC. This particular report focuses on the effects of omega-3 fatty acids on immune-mediated diseases, bone metabolism, and gastrointestinal/renal diseases.

Over the past 40 years, an increasing number of physiological functions have been attributed to omega-3 fatty acids, including movement of calcium and other substances into and out of cells, relaxation and contraction of muscles, inhibition and promotion of clotting, regulation of secretion of substances that include digestive enzymes and hormones, control of fertility, cell division, and growth.[1] In addition, omega-3 fatty acids may play an important role in brain development and function. Some evidence has suggested that omega-3 fatty acids in the diet may protect against heart attack and stroke, as well as certain inflammatory diseases like arthritis, lupus, and asthma.[1] The major dietary sources of omega-3 fatty acids in the U.S. population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat germ, and some dietary supplements.

Methodology

Study Questions

We consulted with three technical expert panels (TEPs) on this project. The respective panels focused on the following conditions: 1) rheumatoid arthritis (RA), systemic lupus erythematosis (SLE), and bone density/osteoporosis; 2) renal disease and diabetes; and 3) gastrointestinal (GI) diseases. The TEPs advised us on refining the preliminary questions posed to us by AHRQ, determining the proper inclusion/exclusion criteria for the study and the populations of interest, establishing the proper outcomes measures, and conducting the appropriate analyses.

Based on the original questions that we received from AHRQ and input from our TEPs, we addressed the following questions in this study:

Diabetes

1.1 What is the evidence in adults or children with a) type II diabetes, or b) insulin resistance/the metabolic syndrome for an effect of omega-3 fatty acids on:

- *total cholesterol*
- *HDL cholesterol*
- *LDL cholesterol*
- *triglycerides*

1.2 What is the evidence in adults and children for an effect of omega-3 fatty acids on insulin sensitivity in a) type II diabetes, or b) the metabolic syndrome?

Inflammatory Bowel Disease

2.1 What is the evidence for the efficacy of omega-3 fatty acids in treatment of Crohn's disease and ulcerative colitis?

2.2 What is the evidence in adults or children with inflammatory bowel disease that omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

2.3 What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of inflammatory bowel disease?

Rheumatoid Arthritis

3.1 What is the evidence that in adults or children with rheumatoid arthritis, omega-3 fatty acids affect:

- *pain*
- *number of swollen joints*
- *disease activity*
- *patients' global assessment*
- *joint damage*

3.2 What is the evidence in adults or children with rheumatoid arthritis that omega-3 fatty acids can replace other more potent anti-inflammatory or immunosuppressive drugs such as steroids and NSAIDs?

3.3 What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of rheumatoid arthritis?

Renal Disease

4.1 What is the evidence for the efficacy of omega-3 fatty acids in treatment of renal inflammation and glomerulosclerosis?

4.2 What is the evidence in adults or children with immune-mediated renal disease that omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

4.3 What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of immune-mediated renal disease?

Systemic Lupus Erythematosus

5.1 What is the evidence that in adults or children with systemic lupus erythematosus, omega-3 fatty acids affect disease activity, damage, or patient perceptions of outcomes in systemic lupus erythematosus(SLE)?

5.2 What is the evidence in adults or children with SLE that omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

5.3 What is the evidence that the benefits of omega-3 fatty acids in the treatment of SLE are influenced by the concomitant administration of various immunosuppressive agents?

Bone Density/Osteoporosis

6.1 What is the evidence that omega-3 fatty acids help maintain bone mineral status?
For each of the study questions, we also assessed 1) the effect of omega-3 fatty acids on sub-populations, 2) the effects of covariates, dose, source, and exposure duration on the outcomes of interest, and 3) the sustainment of effect.

In addition to answering these questions, we evaluated the data on adverse events, including clinical bleeding, gastrointestinal complaints or nausea, diarrhea, headache, dermatological problems, and withdrawal from study due to an adverse event.

Search Strategy

We searched the following on-line databases to identify literature: Medline (1966-July, 2003), Premedline (July 8, 2003), Embase (1980-Week 27, 2003), Cochrane Central Register of Controlled Trials (2nd Quarter, 2003), CAB Health (1973-June 2003), Dissertation Abstracts (1861-to December 2002). We developed a core search strategy and applied it to each relevant disease category: rheumatoid arthritis, bone density, SLE, renal disease, diabetes, and gastrointestinal diseases. We also reviewed the reference lists of all applicable articles and contacted our technical expert panel as well as industry experts to identify unpublished data.

Selection Criteria

Two reviewers independently reviewed each article considered for inclusion in the study. Any disagreements between the reviewers were resolved through consensus. We included any articles pertaining to the effects of omega-3 fatty acids on diabetes mellitus, inflammatory bowel

disease (ulcerative colitis and Crohn's disease), rheumatoid arthritis, SLE, renal disease, osteoporosis, or bone mineral status. We included only articles that presented research on human subjects and those that reported the results of randomized clinical trials, controlled clinical trials; we accepted observational studies only for bone mineral status. Language was not a barrier to inclusion.

Data Extraction and Analysis

For each article included in the study, two reviewers independently extracted data about the trial design; the outcomes of interest; the quality of the trial; the number and characteristics of the patients; details on the intervention, such as the dose, frequency, and duration; the types of outcome measures; adverse events; and the elapsed time between the intervention and outcome measurements. Any disagreements between the reviewers were resolved through consensus. For each article, we then evaluated the quality of the design and execution of trials using a system developed by Jadad; determined a combined applicability grade based on applicability to the U.S. population and health state; performed a meta-analysis of those studies that sufficiently assessed interventions, populations, and outcomes to justify pooling; and performed a qualitative analysis of the remaining studies.

Findings

We screened 4,212 article titles. From these article titles, we reviewed the 1,097 full-text articles relevant to our topics. Of these full-text articles, 115 met our selection criteria and underwent detailed review; among these, 83 articles met our inclusion criteria (34 for diabetes/metabolic syndrome, 13 for inflammatory bowel disease, 21 for rheumatoid arthritis, 9 for renal disease, 3 for SLE, and 4 for bone density and fractures). All of these 83 articles were randomized controlled trials, except for one observational study of bone density. We had a sufficient number of articles to perform quantitative meta-analyses for rheumatoid arthritis, inflammatory bowel disease, and diabetes. Due to the limited number of articles we identified for renal failure, SLE, and bone mineral metabolism, we performed qualitative analyses for these conditions.

Overall, our analyses yielded variable results both within and among disease categories. Our findings are summarized for each condition studied.

Diabetes/metabolic syndrome. Among 18 studies of type II diabetes or the metabolic syndrome, omega-3 fatty acids had a favorable effect on triglyceride levels relative to placebo (pooled random effects estimate: -31.61; 95% CI, -49.58, -13.64) but had no effect on total cholesterol, HDL cholesterol, LDL cholesterol, fasting blood sugar, or glycosylated hemoglobin, by meta-analysis. Omega-3 fatty acids had no effect on plasma insulin or insulin resistance in type II diabetics or patients with the metabolic syndrome, by qualitative analysis of four studies.

Inflammatory bowel disease. Among 13 studies reporting outcomes in patients with inflammatory bowel disease, variable effects of omega-3 fatty acids on clinical score, sigmoidoscopic score, histologic score, induced remission, and relapse were reported. In

ulcerative colitis, omega-3 fatty acids had no effect on the relative risk of relapse in a meta-analysis of 3 studies. There was a statistically non-significant reduction in requirement for corticosteroids for omega-3 fatty acids relative to placebo in 2 studies. No studies evaluated the effect of omega-3 fatty acids on requirement for other immunosuppressive agents.

Rheumatoid arthritis. Among 9 studies reporting outcomes in patients with rheumatoid arthritis, omega-3 fatty acids had no effect on patient report of pain, swollen joint count, ESR, and patient's global assessment by meta-analysis. A previously performed meta-analysis[2] reached the same conclusions for swollen joint count, ESR, and patient's global assessment. That meta-analysis found a statistically significant improvement in tender joint count compared to placebo (rate difference= -2.9, 95% CI –3.8, -2.1). The one study that assessed the effect on joint damage found no effect. In a qualitative analysis of 7 studies that assessed the effect of omega-3 fatty acids on anti-inflammatory drug or corticosteriod requirement, 6 demonstrated reduced requirement for these drugs. No studies assessed the effect on requirements for disease modifying anti-rheumatic drugs. None of the studies used a composite score that incorporates both subjective and objective measures of disease activity, such as the American College of Rheumatology response criteria.

Renal disease. In a qualitative analysis of nine studies that assessed the effect of omega-3 fatty acids in renal disease, there were varying effects on serum creatinine and creatinine clearance and no effect on progression to end stage renal disease. In a single study that assessed the effect on hemodialysis graft patency, graft patency was significantly better with fish oil than with placebo. No studies that assessed the effects of omega-3 fatty acids on requirements for corticosteroids

SLE. Among 3 studies that assessed the effects of omega-3 fatty acids in SLE, variable effects on clinical activity were reported. No studies were identified that assessed effect on damage or patient perception of disease. Omega-3 fatty acids had no effect on corticosteroid requirements in 1 study. No studies were identified that assessed the effects of omega-3 fatty acids on requirements for other immunosuppressive drugs for SLE. None of the studies used a measure of disease activity that incorporates both subjective and objective measures of disease activity.

Bone mineral density/fracture. Among five studies described in 4 reports the effect of omega-3 fatty acids on bone mineral density was variable. No studies that assessed the effect of omega-3 fatty acids on fracture were identified.

The quantity and strength of evidence for effects of omega-3 fatty acids on outcomes in the conditions assessed varies greatly. The findings of many studies among type II diabetics provide strong evidence that omega-3 fatty acids reduce serum triglycerides but have no effect on total cholesterol, HDL cholesterol, and LDL cholesterol. For rheumatoid arthritis, the available evidence suggests that omega-3 fatty acids reduce tender joint counts and may reduce requirements for corticosteroids, but does not support an effect of omega-3 fatty acids on other clinical outcomes. There are insufficient data available to draw conclusions about the effects of omega-3 fatty acids on inflammatory bowel disease, renal disease, SLE, bone density, or fractures or the effects of omega-3 fatty acids on insulin resistance among type II diabetics.

Future Research

We offer the following observations and recommendations regarding future research on the effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis.

1. Additional research on the effects of omega-3 fatty acids need to be performed on inflammatory bowel disease, renal disease, SLE, bone density, or fractures or the effects of omega-3 fatty acids on insulin resistance among type II diabetics before recommendations regarding the use of omega-3 fatty acids for these conditions can be made.

2. Studies of inflammatory bowel disease that include patients with both Crohn's disease and ulcerative colitis should report data separately for these groups.

3. Studies that assess the effects of omega-3 fatty acids should use standard validated instruments to assess clinical outcomes.

4. Trials that assess the effects of omega-3 fatty acids should be designed to evaluate the effect of source, dose, treatment duration, and the sustainment of effect after discontinuation of omega-3 fatty acid consumption.

5. Studies of omega-3 fatty acids should explicitly define both the quantity of the omega-3 fatty acid source and of the specific omega-3 fatty acids present in a study dose of that source.

6. Trials of omega-3 fatty acids should include a baseline assessment of dietary omega-3 and omega-6 fatty acid intake.

7. In controlled trials that assess the effects of omega-3 fatty acids, analysis should include and report explicit testing of the effects of the omega-3 fatty acid relative to the control substance.

8. In studies that use a crossover design, outcome data for all study arms should be reported at the end of each treatment period.

References

1. Innis S. Essential dietary lipids. In: Present knowledge in nutrition. Washington, DC: International Life Sciences Institute; 1996.

2. Fortin P, Lew R, Liang M, Wright E, Beckett L, Chalmers T, et al. Validation of a meta-analysis: The effects of fish oil in rheumatoid arthritis. *Journal of Clinical Epidemiology* 1995;48(11):1379-1390.