Chapter 4. Discussion

Overview

We screened 4,212 titles, from which we reviewed 1,097 full text articles. 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 systemic lupus erythematosus and 4 for bone density and fractures. All articles except one were randomized controlled trials; one was an observational study of bone density.

Most of the studies assessed the effect of omega-3 fatty acids in the form of fish oil; however, some assessed the effect of diets rich in fish. Across all conditions and studies, only 4 studies evaluated omega-3 fatty acids derived from plant oils; three for diabetes [65,66,70] and 1 for RA.[23] Few studies assessed dose or source effect, effect of treatment duration, or the sustainment of effect after discontinuation of omega-3 fatty acid consumption.

Main Findings

Diabetes/metabolic syndrome. Among 13 studies of type II diabetes or the metabolic syndrome, that were assessed by meta-analysis, 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.

These results are consistent with the results of another meta-analysis for fish oil,[116] which found significant triglyceride-lowering and LDL-raising effects and no significant effect on fasting blood glucose, glycosylated hemoglobin, total cholesterol, or HDL cholesterol among diabetics. Although the analysis presented here did not find a significant effect on LDL, the point estimate is consistent with a LDL raising effect and the confidence interval barely crosses null (95% CI, -1.02, 11.25).

The effects of omega-3 fatty acids on triglycerides in diabetics presented here and elsewhere are consistent with the triglyceride-lowering effects of omega-3 fatty acids that have been demonstrated for the general population and are being detailed in a separate evidence report "Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors" (in preparation at the New England Medical Center Evidence Based Practice Center). Regarding the lack of effect that omega-3 fatty acids have on insulin sensitivity, it is possible that any beneficial effects of omega-3 fatty acids on insulin sensitivity could be attenuated by their high calorie content.

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. 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 corticosteroid 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.

A previously performed meta-analysis[97] 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).

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; one study demonstrated less progression to end stage renal disease with omega-3 fatty acids relative to control. 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 or other immunosuppressive drugs for the treatment of renal disease were identified.

Systemic lupus erythematosus. 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.

Dose, source, duration effects and sustainment of effect. Among studies that assessed the effects of omega-3 fatty acids in diabetes, there was no dose effect for any outcome by meta-regression. There are insufficient data to draw conclusions about source or duration effects, or about sustainment of effect.

Adverse events. Across all conditions, the incidence of gastrointestinal complaints or nausea, diarrhea, and headaches appears to be higher among patients receiving omega-3 fatty acids than among those in control groups. Strong conclusions cannot be drawn from this

observation because adverse events were not reported in a standard manner in clinical trials, either in terms of the events defined or the frequency with which they were recorded. Additionally, the underlying conditions being studied will affect the rates of specific adverse events.

Conclusions

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.