

FISH OIL SUPPLEMENTATION IN PEOPLE WITH DIABETES: A REVIEW OF THE RESEARCH

Gretchen K. Vannice, MS, RD
Jill Kelly, Ph.D.

The *World Health Organization* and the *International Diabetes Federation* have recently reported that 3.2 million deaths a year (1) can be attributed to diabetes, a complex condition of related metabolic disorders, including dyslipidemia, as well as a high risk of cardiovascular complications. Indeed cardiovascular disease has been confirmed as the major cause of death in people with both type 1 and type 2 diabetes (2). Recently, the role of supplementation of long-chain omega-3 (ω -3) fatty acids from fish oil in the management and treatment of both insulin-dependent diabetes mellitus (type 1 DM) and non-insulin-dependent diabetes mellitus (type 2 DM) has been the subject of numerous clinical trials.

First, research shows that fish oil supplementation significantly lowers triglyceride levels. A 1998 meta-analysis of 26 trials of fish oil supplementation in people with diabetes (both type 1 and type 2) that analyzed their serum lipids and glucose tolerance showed a decrease of almost 30% in triglyceride (TG) levels (3). The authors concluded that 3 g/day (the dose most commonly used) of ω -3 fatty acids was a safe and effective dosage for lowering TG levels in people with type 2 DM. A second meta-analysis (4) in 2000 of 823 diabetic subjects (mostly type 2 men between 55–65 years of age), which included some of the same trials, found comparable results: fish oil supplementation significantly lowered triglycerides (weighted mean: -0.56mmol/l), especially in those with hypertriglyceridemia (weighted mean: -0.73 mmol/l). The authors of the 2000 review con-

cluded that fish oil supplementation is a helpful and reasonable therapeutic strategy in patients with high TG levels; in addition, they reported that in those with normal TG levels, no clinically significant effects on glycemic control were found (4).

While the triglyceride-lowering effect of fish oil supplementation is consistently found in clinical trials, the impact of these ω -3 fatty acids on LDL-cholesterol (LDL) is less clear but still promising. For example, in the 1998 review cited above, LDL levels were raised only slightly, but significantly, in type 2 DM subjects (mean change 0.20 mmol/l) (3). The findings in the 2000 review also showed an increase in LDL levels (average of 0.21mmol/l) (4). Contradicting both these findings, a related randomized, double-blind, placebo-controlled study of 51 men and women with type 2 DM taking either 4g EPA or DHA (the principal fatty acids of fish oil) or olive oil found that no significant changes in total cholesterol, LDL, or HDL occurred (5). Similarly, in an 8-week placebo-controlled trial of randomized groups of 42 subjects with type 2 DM who were administered 4g/d of fish oil or corn oil, the results showed lowered TG and raised HDL_{2b} levels but no significant effects on LDL or HDL (6). However, in a review of 36 crossover and 29 parallel studies comparing the essential fatty acids (EFAs) in flaxseed oil and fish oil, total cholesterol was not materially affected by ω -3 fatty acids but LDL tended to rise 5–10% and HDL by 1–3%, while serum TG concentrations decreased by 25–30% (7). (The authors also noted that very large amounts of

flaxseed oil were needed to reduce TG levels to the levels that fish oil did).

Fish oil also has a favorable impact on blood pressure. In a clinical trial of 19 obese, hypertensive, and dyslipidemic patients with diabetes (OHD+DM) or without (OHD-DM), a 13-day protocol of programmed fasting and fish-oil feeding (8) lowered BP in both groups, from 159/81 to 146/73 mmHg in the OHD-DM group, and 158/83 to 142/76 mm Hg in the OHD+DM group. Serum TG levels were also reduced, from 159 to 108 mg/dl in the OHD-DM group, and from 209 to 153 mg/dl in the OHD+DM group. In addition, HDL increased significantly in the OHD+DM group. A favorable reduction in hemostasis parameters (platelet aggregation) was seen among the non-diabetic patients only (8). Similarly, a meta-analysis of 36 trials of fish oil supplementation (median dose 3.7 g/d) and blood pressure in adult men and women showed that fish oil has a small hypotensive effect on BP, especially in those who are older and have hypertension. The mean duration of these trials was 11.7 weeks. The mean reductions in blood pressure were significant, with systolic being reduced by 2.1 mmHg and diastolic reduced by 1.6 mmHg (9). It has been shown that even relatively small BP reductions may reduce stroke and coronary event risk (10).

Lastly, fish oil seems to have a beneficial effect on endothelial function, either by decreasing endothelial activation or by improving endothelium-dependent vasodilation in patients who are at high risk for cardiovascular disease, including those with diabetes (11). How ω -3 fatty acids are atheroprotective is unclear; however, they appear to influence lipid concentrations, as we have seen, as well as the size and oxidizability of lipids, platelet aggregation (12), and arrhythmia (13).

All of these lipidemia factors may well explain why a prospective study of 5,103 female nurses with type 2 DM but free of cardiovascular disease at baseline showed that those diabetic

women with higher consumption of fish and fish oil supplementation had a lower rate of coronary heart disease and total mortality (14).

There has been concern that fish oil supplementation may raise blood glucose levels. However, evidence suggests that there may be no reason for concern, particularly in a risk-benefit analysis. No significant effects on blood glucose levels were seen in the 2000 meta-analysis, involving 18 trials and >800 type 2 DM subjects (4). And while the 1998 study showed small but borderline significant ($p = 0.06$) increases in fasting blood glucose levels in the type 2 DM subjects (and a lowering of fasting blood glucose levels in the type 1 DM subjects), the authors concluded that 3 g/day of ω -3 fatty acids were safe and effective for lowering TG levels in patients with diabetes (3). Furthermore, in a randomized double-blind crossover of 12 type 2 diabetic men who took 6g daily of fish oil or sunflower oil for 2 months, results showed fasting plasma insulin, glucose, and HbA_{1c} levels were similar in the two groups, and there was no increase in basal hepatic glucose production (15). In another study of 16 type 2 DM patients with hypertriglyceridemia who were randomly assigned to either fish oil (2.7g/d for 2 months, then 1.7g/d for 4 more months) or olive oil, there was a long-term significant reduction in plasma TG and VLDL-TG, a significant enrichment in the erythrocyte phospholipid content of long-chain ω -3 fatty acids, and no deterioration of blood glucose control (16). No changes in the variables were observed in the placebo (olive oil) group. The authors did note that this amount of ω -3 fatty acids was unable to improve insulin resistance in the subjects (16). And the *Italian Fish Oil Multicenter Study* (17), a randomized double-blind placebo-controlled study evaluated the possible worsening of glycemic control after fish oil supplementation in hypertriglyceridemic patients with and without glucose intolerance or diabetes. A total of 935 adult men and women were given 3 g/day (1 g, 3x/d) of ω -3 fatty acids for 2 months or placebo, then 2 g/day (1 g, 2x/d)

for 4 months or placebo. As expected, there was a significant decrease in triglycerides (21.53% at 6 months with a tendency toward a progressive reduction over time); in addition, there was no alteration in the major glycemic indexes, including fasting glucose levels. What's more, in the subgroup with diabetes, no alterations in HbA1c or serum insulin were noted. And finally, the subgroup with impaired glucose tolerance underwent oral-glucose-tolerance tests before and after the study period; no alterations were seen following the supplementation (17).

In summary, in people with diabetes, multiple human clinical trials have shown that fish oil supplementation significantly reduces triglyceride levels, improves HDL levels, reduces blood pressure by a small yet significant amount, and does not adversely affect blood glucose levels. Furthermore, fish oil supplementation, especially from purified sources, has been noted to be safe and effective by several investigators. The diverse and beneficial effect of fish oil supplementation on the many aspects of diabetes makes supplementation a promising therapeutic.

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