Fish Oil for Treatment of Hypertriglyceridemia in HIV Infection: Fish or Foul?

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(See the article by Wohl et al. on pages 1498–504)

Wohl et al. [1] have written an important article presenting a randomized trial of fish oil, a nutraceutical, for the treatment of hypertriglyceridemia in HIV-infected patients who are receiving antiretroviral therapy. To understand whether this therapy is “fish or foul,” one must keep several questions in mind. What is being treated? What is the target level for triglycerides? Did it work? Were there side effects? How does the therapy compare with the alternatives? Where do we go from here?

Fish oil is a treatment for hypertriglyceridemia, not for hypercholesterolemia. Although in the study by Wohl et al. [1], enrollment criteria were hypertriglyceridemia and receipt of antiretroviral therapy, the causes of high triglyceride levels in the HIV-infected population are manifold. They include HIV infection itself; antiretroviral therapy (especially with ritonavir and perhaps with stavudine); HIV-infection–specific changes in fat distribution, such as lipoatrophy; increased visceral adipose tissue, which is independent of lipoatrophy; and the factors that affect all populations, such as obesity, inactive lifestyle, fructose in the diet, alcohol, diabetes, and genes [2]. The additive or synergistic effects of these factors often make treatment of hypertriglyceridemia a challenge in the HIV-uninfected patient. That is compounded in the HIV-infected patient.

Fasting triglyceride levels of >500 mg/dL are associated with risk of pancreatitis [3, 4]. Levels of >150 mg/dL may be associated with cardiovascular disease [5]. It is difficult to reduce the triglyceride level when it is >500 mg/dL at baseline, as was the case in many of the patients in this study. The higher the starting level, the more difficult it is to reach the goal level, and the more likely the need for polypharmacy. Fish oil achieved a nice reduction in mean triglyceride levels, from 461 mg/dL at 4 weeks. At 16 weeks, the lower levels were sustained, but study dropouts and the usual fluctuations in triglyceride levels reduced the statistical significance of this finding. These triglyceride levels were still, unfortunately, above the level for cardiovascular risk.

However, the level of reduction achieved by fish oil supplementation is all we could have expected and is similar to that achieved by other agents, such as fibrates and niacin [6, 7]. In the HIV-uninfected population, very high triglyceride levels are treated first with dietary counseling, including recommendations to minimize the intake of fructose and alcohol, as well as to introduce a low-fat diet (as opposed to a low–saturated fat diet, which is used to treat hypercholesterolemia). Fish oil is the only fat that lowers triglyceride levels; olive oil lowers cholesterol, but in excess it will raise triglyceride levels. Then the clinician starts treatment with fibrates, niacin, and/or fish oil, hoping to get results like those seen in Wohl et al. [1] and knowing that further treatment will likely be needed for many hypertriglyceridemic patients.

The toxicities in this study were minimal but are important to understand. One of 26 subjects receiving fish oil withdrew because of dislike of the formulation. Fish oil tastes like fish, it can make you smell like fish, and it can cause you to burp the same fish smell. Another subject withdrew because of nausea and vomiting, which remitted after treatment with fish oil was discontinued. Fish oils do cause nausea in some patients. Excess bleeding from the effects of fish oil on platelets is a toxicity that relates to one of the ways that fish oil prevents myocardial infarction, but this was not seen in this small trial.

Low-density lipoprotein (LDL) levels rose by a mean of 22% in these patients. As stated above, fish oil does not treat hypercholesterolemia. Rises in LDL levels are expected in fish oil trials, especially in patients with low LDL levels at the outset, but the increases are usually in the range of 5%–10% [8]. Given that LDL levels are...
low in people with HIV infection and are increased by antiretroviral therapy, an anti-inflammatory effect of fish oil in HIV infection may compound the usual effects of fish oil on LDL levels. Fish oil is not unique in increasing LDL levels in patients with hypertriglyceridemia; fibrates also raise LDL levels [6, 7]. Given the need for polypharmacy for both hypertriglyceridemia and HIV infection itself, one would like not to add a statin to the treatment regimen, but a high percentage of HIV-infected patients receiving antiretroviral therapy are already being treated with statins. Although niacin induces less of a rise in LDL levels and produces a beneficial increase in high-density lipoprotein levels, niacin induces insulin resistance and may precipitate or modestly worsen diabetes [7, 9, 10]. Glucose intolerance and diabetes are also an increasing problem in HIV infection [2]. The flushing caused by niacin leads to even higher treatment discontinuation rates.

We are therefore left with a therapy that works well (“fish”), but not well enough and has side effects (“foul,” albeit some foul side effects are fishy). Nevertheless, in this study of HIV-infected patients, fish oil therapy looks like it is as good as the other possible therapies. It potentially adds another powerful agent to our armamentarium. It will no doubt be used in combination with other therapies, as is often the case in HIV-uninfected subjects; however, the toxicities are complex, because fibrates and statins may synergize to cause rhabdomyolysis [11]. As Wohl et al. [1] point out, we do need larger studies, some of which should test higher doses, and there are no double-blind studies. In the case of fish oil, a study can be blinded at the capsule level, but would difficult to “blind” at the smell level. I would also urge that larger studies be done, including studies of combination therapy, as larger studies are the only way to understand toxicity in this complex world of polypharmacy for HIV infection.

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References

9. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease, the ADMIT study—a randomized trial. Arterial Disease Multiple Intervention Trial. JAMA 2000;284:1263–70.