



A Randomized, Open-Label Trial of Omega-3-Fatty Acid (Fish Oil) Supplementation Along with Diet and Exercise in HIV+ Patients with Hypertriglyceridemia

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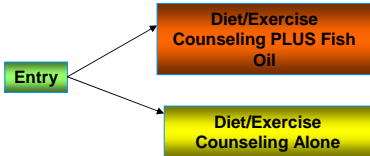


Introduction

- Hypertriglyceridemia is common among HIV-infected persons and, along with elevation of LDL cholesterol, has been observed to be exacerbated by antiretroviral therapy.
- Recent reports suggest combination antiretroviral therapy may increase the risk of cardiovascular disease.
- Omega-3 fatty acids have been shown in epidemiological and clinical trials to reduce the incidence of CVD¹ and prospective secondary prevention studies suggests that marine-derived omega-3 fatty acid (EPA+DHA) supplementation ranging from 0.5 to 1.8 g/d (either as fatty fish or supplements) significantly reduces subsequent cardiac and all-cause mortality².
- The American Heart Association (AHA) recommends persons with coronary heart disease consume ~1 g of omega-3 EPA+DHA (fish oil) per day, preferably from oily fish or via supplementation if dietary intake is insufficient. Patients with hypertriglyceridemia may consider supplementation with 2-4 g/d of EPA+DHA³.
- The efficacy and safety of omega-3 fatty acid supplementation for hypertriglyceridemia in the setting of HIV infection is not known.

Methods

Design: Randomized controlled open-label 16 week trial.



- Interventions:**
- Omega-3 fatty acid: Coromega® (European Reference Botanical Laboratories Inc.) containing 1750 mg EPA + 1150 mg DHA mg was administered orally daily. This formulation is a liquid and was chosen due to its pleasant taste and available bioavailability data
 - Diet and Exercise Counseling:** Certified nutritionist-administered individual counseling in accordance with American Heart Association recommendations for diet and exercise were conducted at Entry and weeks 4 and 16

Methods (cont)

- Inclusion Criteria:**
- Fasting serum triglycerides 200-2000 mg/dL
 - Stable HAART for 3 months
 - Not receiving a fibrate
 - If receiving a statin, to remain on agent without modification during the study
 - Karnofsky status score ≥70
- Evaluations at Entry and Week 4 and Week 16:**
- Fasting (> 8 h) triglycerides, total, LDL and HDL cholesterol – UNC Clinical Lab
 - Direct LDL cholesterol, Lp(a) – VAP (Atherotech Inc.)
 - 2h Oral Glucose Tolerance Test UNC Clinical Lab
 - Platelet Function Assay – UNC Clinical Lab
 - AACTG Self-Reported Adherence Survey

Statistical Methods:
The primary objective was to compare the change in fasting triglyceride levels at week 4 among subjects randomized to Diet/Exercise alone versus with the addition of Fish Oil.
For the primary analysis triglyceride values were log transformed and the paired t-test employed. For descriptive purposes, the original values were also analyzed prior to transformation to logarithm. Inter and intra-arm comparisons were performed.

Results

- 52 subjects were randomized
- 8 subjects were lost to follow-up prior to week 4

Table 1 • Mean Baseline Characteristics

	Fish Oil (n=25)	Diet/Exercise (n=19)
Male (%)	88%	95%
Age (y)	42 (25-58)	44 (36-54)
Non-white (%)	64%	42%
Triglycerides (mg/dL)	454	553
Total Cholesterol (mg/dL)	230	254
HDL-C (mg/dL)	40	42
LDL-C (mg/dL)	112	117
Lp(a) (mg/dL)	10	12
CD4 cell count (/uL)	576	505
HIV RNA (log ₁₀ c/mL)	38618	35110

Fig. 1 • Mean Percent and Log Change from Baseline in Triglyceride Levels

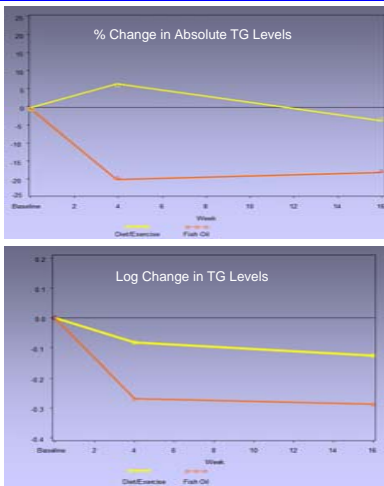


Table 2 • Mean Percent Change from Baseline in Triglycerides

	Fish Oil (95% CI)	Diet/Exer. Alone (95% CI)	P value between arms
Wk 4	-19.6% (-30.1, -9.0)	+6.4% (-23.3, +36.2)	0.049
Wk 16	-17.7% (-33.4, -2.0)	-3.5% (-25.7, +18.7)	0.134

Table 3 • Proportion of Subjects in Each Arm with Triglyceride Level <200 at weeks 4 and 16

	Fish Oil	Diet/Exercise Alone	P value
Wk 4	9 (36%)	2 (11%)	0.046
Wk 16	6 (27%)	4 (26%)	0.279

Fig. 2 • Mean Percent Change from Baseline in Total & LDL Cholesterol Levels

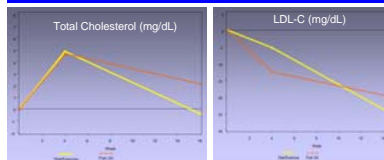


Table 4 • Mean Percent Change from Baseline in LDL, Total Cholesterol, Lp(a) Insulin and 2h OGTT Result

	Fish Oil	Diet/Exercise Alone
LDL-C Wk 4	-12.6% (-24.8, -0.3)	-5.3% (-20.0, +9.4)
LDL-C Wk 16	-21.0% (-38.2, -3.8)	-27.5% (-54.3, -0.7)
Total Cholesterol Wk 4	+4.7% (-1.1, +10.5)	+4.7% (-3.4, +13.1)
Total Cholesterol Wk 16	+2.1% (-7.5, +11.7)	-0.4% (-11.8, +10.9)
Lp(a) Wk 4	-0.3% (-114.7, +34.1)	+0.8% (-31.4, +32.9)
Lp(a) Wk 16	-4.5% (-115, +22.1)	-2.2% (-37.3, +32.9)
Insulin Wk 4	82.56% (+7.2, +158.0)	31.0% (-29, +90.9)
Insulin Wk 16	24.33% (-20.9, +69.5)	127.1% (-96, +350.2)
2 h OGTT Wk 4	-3.7% (-12.7, +5.4)	6.4% (-9.2, +22.0)
2 h OGTT Wk 16	-1.0% (-9.1, +7.2)	-3.7% (-12.7, +5.4)

Fish Oil Self-Reported Adherence

- At week 4: 82.6% reported not missing fish oil in past 4 days
- At week 16: 87.0% reported not missing fish oil in the past 4 days

Safety and Tolerability

- Fish oil was well tolerated:
 - No new grade 3+ clinical or laboratory toxicities
 - 1 subject discontinued Fish Oil due to nausea and vomiting associated with the agent
 - No change in platelet function assay results
 - No change in viral load or CD4+ cell count

Conclusions

- Fish oil supplementation at a dose of ~3 grams/d coupled with diet and exercise counseling modestly reduced triglycerides in HIV-infected patients.
- However, a statistically significant difference in the decline of triglyceride levels was not observed between those assigned to diet/exercise counseling without fish oil supplementation in this small study.
- Fish oil was well tolerated. One subject had a treatment-limiting adverse event. No subject developed a grade 3 or higher clinical or laboratory toxicity.
- Given the trends observed in this pilot study, larger trials of fish oil supplementation for the treatment of HIV-associated hypertriglyceridemia are warranted.

References

- Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio del Sopravvivenza nell'Infarto miocardico. *Lancet*. 1999; 354: 447-455
- Bucher HC, Hengstler P, Schindler C, et al. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2002; 112: 298-304
- AHA Scientific Statement: Fish Consumption, Fish Oil, Omega-3 Fatty Acids and Cardiovascular Disease, #71-0241 *Circulation*. 2002;106: 2747-2757

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