Changes in Total Homocysteine Levels Following Supplementation of Omega-3 Fatty Acids in End Stage Renal Disease Patients

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Abstract

Aim: Vascular damage and premature atherosclerosis occurs when arterial endothelium is exposed to elevated levels of homocysteine. The purpose of this study was to examine the effect of an over-the-counter (OTC) Omega-3 fatty acid (n-3) supplementation on total homocysteine (tHcy) levels in ESRD patients undergoing chronic hemodialysis. **Methods**: A permuted-randomized, double-blind and placebo controlled experimental protocol was used. End-Stage-Renal Disease (ESRD) patients (N=69) were followed prospectively while supplementing fish oil (treatment [n-3]) or corn oil (placebo [n-6]) for six months. tHcy was obtained through whole blood analysis at baseline and at six months. **Results**: The results of this study using regression models revealed differences in age and gender regarding homocysteine levels at the posttest (six months). Study findings contradicted previous published work with the present study findings suggesting that daily administration of n-3 fatty acids containing 160 mg of EPA (0.96 g/day) and 100 mg of DHA (0.6 g/day) had no effect on tHcy levels when compared to control. **Conclusion**: Published findings regarding the relationship between n-3 supplementation and tHcy have been equivocal and appear to vary based on sample population, n-3 dosage, and study duration. Potential reasons for the non-significant result of this study may be found in a dose-response relationship, as well advancement of disease progression in the sample population. This study did not support the work of previously published study authors who supplemented 4 grams per day with a higher dose of EPA (1.75 grams) and DHA (0.96 grams) using a pharmaceutical grade n-3 possibly creating a smaller dose-response in the present study. Secondly, ESRD patients have progressed morbidity making the lowering of tHcy problematic and may cause patients to not be responsive to a lower dosed OTC n-3 supplement. Hyperhomocysteinemia was elevated for a prolonged period of time in this patient population with supplementation possibly occurring too late in the morbid condition. Future studies should continue to focus on the OTC n-3 supplements to save out of pocket expenses for patients and decrease utilization of pharmaceutical treatments.

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with renal failure. In addition to many of the established risk factors for CVD in the general population, end stage renal disease (ESRD) patients also present with uremia-specific risk factors, such as volume overload with consequent hypertension, anemia, altered calcium-phosphate metabolism, elevated levels of specific uremic toxins, and chronic inflammatory processes. Specifically, elevated levels of the uremic toxin homocysteine (tHcy) has been shown to be a strong predictor of cardiovascular events in patients with preexisting morbid conditions such as renal failure. This is of particular concern for the ESRD population, as approximately 85-100% of ESRD patients will develop hyperhomocysteinemia post kidney failure.

Study authors have suggested the mechanisms for reduced tHcy concentrations may be attributed to possible FO-induced oxidative stress and stimulation of the oxidative catabolism of tHcy, the alteration of cysteine/tHcy ratios via the transsulfuration pathway, and the inhibition of methionine synthase activity with FO supplementation by way of enhanced nitrous oxide production.

Only a small number of study authors have published the effects of FO supplementation on tHcy, with equivocal findings reported. Therefore, the purpose of this study was to examine the effect of an over the counter (OTC) n-3 supplementation on tHcy levels in ESRD patients undergoing chronic hemodialysis.

Experimental Design

Participants

- ESRD patients (N=69) 18 years of age and older were recruited for the study
- Participants were informed as to the experimental procedures and signed informed consent statements in adherence with the human subjects guidelines with Baylor University

Study Protocol

- The study was conducted using a triple-blind, permuted-block randomized and placebo controlled experimental design.
- Subjects were randomly assigned to:
  - Fish oil group (n=35) [treatment]
  - Corn oil group (n=34) [placebo]

Methods

Patients in the experimental group consumed two 1-gram softgel capsules of fish oil concentrate with each meal or six capsules (6 grams) per 24 hours. The control group consumed two 1-gram softgel capsules of corn oil with each meal or six capsules (6 grams) per 24 hours, following the same protocol as the n-3 fatty acid group. Outcome variables were measured at baseline and six months. Additionally, all patients consumed vitamin supplements which contained 15 mg of B_6, 12 mg of B_{12}, and 2.5 mg of Folic Acid.

Fish Oil and Placebo Composition

Fish oil and placebo were quality assured and quality controlled by *Royal Numico Research B.V.* (Greenville, SC). Fish oil soft-gels were packaged in a 1-gram capsule which contained 160 milligrams of EPA and 100 milligrams of docosahexaenoic acid (DHA) and 0.9 IU of d-alpha tocopherol as an antioxidant. The placebo soft-gels were packaged in a 1-g capsule which contained Canola oil (94% unsaturated fat, 6% saturated fat).

Statistical Analysis

All statistical analyses were performed using SAS software (version 9.1.3; SAS Institute Inc, Cary, NC). All statistical tests were performed at the two-sided alpha level of 0.05 to determine significance. Baseline values were compared using t-tests for continuous data and chi-square tests for categorical data. The comparison of the change of mean values of tHcy between the two groups at 6 months used a 1-factor ANOVA analysis. To analyze a statistical model with additional covariates, we utilized three stepwise linear regression models to test the significance of both the covariates and their interactions with the treatments.

Results

There was no observed statistically significant difference between the treatment and control groups at baseline regarding age, gender, tobacco history, diabetic status, months on dialysis, and tHcy levels. Likewise, no differences were observed between the two groups in the mean changes from baseline to 6 months or between the two groups' tHcy values at 6 months.

Discussion

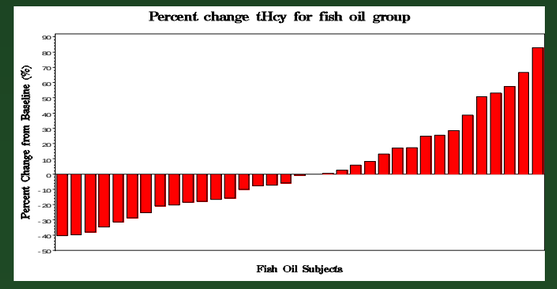
The results of our study demonstrate that the administration of OTC FO supplementation was no better than a placebo in lowering tHcy levels in an ESRD population. Potential reasons for this non-significant result may be found in a dose-response relationship, advancement of disease progression in our sample population, or potentially the lack of a significant relationship between fish oil and tHcy. Future studies should seek to clarify the mechanism by which omega-3 fatty acids may lower tHcy levels, address whether a dose-response relationship between n-3 fatty acid supplementation and tHcy levels exists, and examine how stage of disease progression affects intervention success or failure.

Tables/Figures

Table 1: Outcome change measures of fish oil supplementation on plasma homocysteine concentrations (unadjusted means).

Group	Control Group (95% CI)	Fish Oil Group (95% CI)	2-sided P-Value
tHcy at 6 months,	28.11 (23.62, 32.61)	30.11 (26.33, 33.87)	0.49
tHcy change from baseline,	1.58 (-2.85, 6.01)	0.01 (-3.05, 3.07)	0.55
Percent tHcy Change from baseline	12.7% (-4.36, 29.79)	3.24% (-7.73, 14.21)	0.32

Figure 1: Changes in tHcy values in the experimental group.



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