The Effects of Fish Oil Supplementation on Lipid Levels in Non-Hemodialysis Chronic Kidney Disease Patients

Paul La Bounty¹, Rodney G. Bowden¹*, Erika Deike², Jennifer J. Moreillon¹, Jackson O. Griggs³, Ronald L. Wilson⁴ and Brian D. Shelmadine¹

¹Baylor University, Waco, TX, USA.
²Texas Lutheran University, San Antonio, TX, USA.
³Family Health Center, Waco, TX, USA.
⁴Central Texas Nephrology Associates, Waco, TX, USA.

ABSTRACT

Aims: The purpose of the study was to examine the effects of a moderate dose of commercially available fish oil on lipid variables in non-hemodialysis, chronic kidney disease patients.

Study Design: The study utilized a double-blind, randomized, and placebo-controlled experimental design. The experimental intervention consisted of fish oil supplementation or a safflower oil control.

Place and Duration of Study: Patients (N=31) from a family medicine center with Chronic Kidney Disease were eligible for the study and followed prospectively for eight weeks.

Results: ANCOVA revealed a significant difference at post-test (p=0.02; Cohen’s d=−0.58) in HDL. No significant differences at post-test for triglycerides (p=0.66; Cohen’s d=−0.20).

Authors’ contributions

This work was carried out in collaboration between all authors. Author PLB created the initial draft and approved the final draft. Authors RGB, ED, JJM, JOG, RLW and BDS designed the study, wrote the protocol and approved the final draft. Author RGB conducted the statistical analyses. Authors ED and JJM conducted the literature review. All authors read and approved the final manuscript.

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*Corresponding author: Email: Rodney_Bowden@baylor.edu;
d=0.16), total cholesterol (p=0.84; Cohen's d=-0.04), LDL (p=0.39; Cohen’s d=0.25), total cholesterol/HDL ratio (p=0.34; Cohen’s d=0.20), and ApoB (p=0.52; Cohen’s d=0.11) were discovered.

**Conclusions:** The results of our study suggest the consumption of 2.4 grams of combined EPA and DHA may be an effective over-the-counter nutritional intervention to increase HDL in individuals with CKD. The reasons for non-significant findings in all other cholesterol variables may be due to a dose-response relationship, the short duration of the study, the study population, or the supplements simply may not be effective in improving these variables.

**Keywords:** Cholesterol; high density lipoprotein; low density lipoprotein; triglycerides; omega-3 fatty acids.

### 1. INTRODUCTION

It has been estimated that approximately 19 million American adults have chronic kidney disease (CKD) [1] and some will eventually develop chronic renal failure (CRF) also known as end-stage renal disease (ESRD). CKD patients have an increased incidence of hospitalization, cardiovascular disease, and premature mortality [1,2] with cardiovascular complications the leading cause of death in this population [3]. Specifically, Prichard [4] has reported patients with CKD often have relatively normal levels of low density lipoprotein cholesterol (LDL), but have elevated triglycerides, decreased high density lipoprotein cholesterol (HDL) and can have limited success with lipid lowering therapy which is primarily due to proteinuria rather than the state of CKD. Therefore novel treatments for CKD patients are warranted.

One such therapy is the intake of polyunsaturated omega-3 fatty acids (n-3) which has been reported to have positive effects on lipids and inflammatory cytokines in individuals with CKD [5,6]. It has also been hypothesized that low total plasma polyunsaturated fatty acid levels in older adults may be associated with a more rapid decline of overall kidney function [7]. The two primary long chain polyunsaturated n-3, commonly referred to as fish oils, are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [8]. These fatty acids can be consumed through the diet by ingesting oily, cold water fish, such as salmon and mackerel or through dietary fish oil supplementation. Globally, the n-3 appear to significantly affect several physiological parameters in humans such as assorted metabolic pathways, cell membrane physiology, and various inflammatory and immune responses [8]. Specifically, n-3 may decrease blood pressure, help maintain dialysis access patency, and mitigate inflammation-associated muscle loss [8].

The consumption of a relatively moderate intake of n-3 (1.5-2.4 g/d) over 8-weeks has been reported to improve the lipid profile in ESRD patients [2,9]. Khajehdehi [9] reported a significant decrease in both serum triglycerides and LDL as well as an increase in HDL following 2 months of consuming 1.5 g/day of fish oil in hemodialysis patients. Another study examining CKD patients reported a significant decrease of 21% in serum triglycerides and a significant increase of 8% in serum high-density lipoprotein cholesterol levels in those that consumed 2.4 g of n-3 as compared to olive oil for 8 weeks [2]. However, there were no significant changes in either LDL or total cholesterol for either group [2].

Other studies have given larger amounts of fish oil to CKD patient populations as well. Bowden et al. [10] administered either 6 g/d of fish oil concentrate or corn oil in ESRD
patients undergoing hemodialysis for 6 months. The investigators reported that HDL significantly increased in the fish oil group while decreasing in the corn oil group [10]. Interestingly, however, LDL cholesterol significantly increased in both groups [10].

In the United States, it has been reported that only 0.1-0.2 g of combined EPA and DHA are consumed daily [11] and to date, there are no definitive n-3 intake recommendations for individuals with CKD [8]. However, it has been suggested that the amount recommended by the American Heart Association for individuals with coronary heart disease (1 gram of EPA + DHA) may be acceptable in CKD patients [8]. Currently, however, it is believed that patients with CKD do not have adequate blood levels of DHA and EPA [12]. This is most likely due to suboptimal dietary intake.

Although there have been several studies that have investigated the effects of fish oil on lipid variables in exclusively ESRD patients, [2,3,9,10] less has been studied about the effects of over the counter fish oil consumption in non-dialysis CKD patients. Therefore, the purpose of this study was to investigate the effects of daily fish oil supplementation compared to a placebo on various lipids in non-dialyzed patients with CKD.

2. METHODOLOGY

Exclusionary criteria included patients who had taken an omega-3 supplement within the last three months, had allergies for fish or safflower oil, had a current involvement in another dietary study, an active illness requiring hospitalization, life expectancy was less than three months, presence of malabsorption syndromes, pregnancy, had any change in body weight (≥ 10 lbs.) in the past six months, or had a previous history of medication non-compliance. Patients age 18 yrs. and older meeting eligibility criteria were informed of the requirements of the study and signed informed consent statements were taken in compliance with the University Institutional Review Board and the family medical clinic.

2.1 Experimental Design

A sample size of 31 (16 males and 15 females) participated in the study which was conducted using a double-blind, randomized, and placebo-controlled experimental protocol. Participants meeting entry criteria were familiarized to the study protocol by way of a verbal and written explanation outlining the study design. During the baseline and posttest testing sessions, a side-effect questionnaire was completed and the participants' weight, blood pressure, and heart rate were assessed. Additionally, a blood draw after a 12 hour fast was obtained at both testing sessions. Participants were randomized to receive either a dietary fish oil supplement (experimental, n=17) or a placebo (safflower oil, n=14) and were given an 8-week supply of the respective supplement. The experimental group was instructed to orally ingest 2 soft-gel capsules of n-3 supplements with morning and evening meals for daily totals of 1400 mg of EPA and 1000mg of DHA. Therefore, patients consumed a total of 2.4g of omega-3 fatty acids (EPA + DHA)/day. The control group participants were assigned to orally ingest 2 soft-gel capsules containing the placebo at both morning and evening meals. After the 8-week supplementation protocol, the participants returned for their final testing session. Throughout the 8-week protocol, participants were called weekly to verify that they were taking their supplements on a regular basis. Supplementation compliance was also monitored by having the subjects return supplement bottles with any remaining pills at the end of 8-weeks of supplementation. The standard practice of pill counting was used to assess compliance. It has been reported by study authors that the standard for compliance
is between 80 and 100% [13]. Therefore, patients that consumed 80% of the issued supplements in this study were considered compliant. All supervised data collection was conducted at a family medicine clinic under the guidance of their treating physicians.

2.2 Fish Oil and Placebo Composition

Fish oil and placebo were quality assured and quality controlled by Life Extension and was provided for this study (Ft. Lauderdale, FL). Both fish oil and placebo capsules were 1 gram each. One capsule contained 350 mg of EPA, 250 mg of DHA, 150 mg of Olive Fruit Extract, and 5 mg of Sesame Ligan Extract. The placebo was composed of safflower oil, high in unsaturated omega-6 fatty acids. Safflower oil has been used as the placebo in other n-3 fatty acids studies [14,15].

2.3 Body Mass, Height, and Hemodynamic Safety Markers

Body mass was measured at baseline and 8-weeks later. Measurements were assessed using a digital scale accurate to ±0.02 kg. Heart rate and blood pressure was assessed in the seated position using a blood pressure monitor.

2.4 Reported Side Effects from Supplements Questionnaire

At the conclusion of each week during the study, participants reported by questionnaire how well they tolerated each supplement. In addition, participants were told to report any medical problems/symptoms they may have encountered throughout the duration of the study through weekly phone calls. However, if symptoms/complications were to arise prior to completing the questionnaire, participants were encouraged to report them as they occurred.

2.5 Blood Lipid Analysis

Participants donated approximately 50 milliliters of blood for lipid analysis at baseline and at 8-weeks. Blood samples were obtained after a 12-hour fast and standardized to the same time of day for each sample. Blood samples were obtained via the antecubital vein using standard phlebotomy procedures and were analyzed at Quest Diagnostics Laboratory (Dallas, TX) using standard gel electrophoresis techniques for a standard lipid panel of triglycerides, HDL, LDL, total cholesterol, total cholesterol/HDL ratio, apolipoprotein B (ApoB), high sensitivity C-reactive protein (CRP) and albumin.

2.6 Statistical Analysis

The Statistical Package for the Social Sciences for Windows (version 18.0, SPSS Inc, Chicago, IL) was used to perform the statistical analysis of the data. Statistical significance was set a priori at .05. The primary outcome variables of interest were serum triglycerides, total cholesterol, HDL, LDL, total cholesterol/HDL ratio, and ApoB. Analysis of variance (ANOVA) was used to measure whether there were pretest differences in age, weight, waist circumference, serum lipids, albumin, and C-reactive protein (CRP). Analysis of covariance (ANCOVA) was used to assess differences in all serum lipids while controlling the potential covariates of body mass, waist circumference, albumin, CRP, and dietary supplement compliance. Cohen’s d was utilized to assess effect size of all the serum lipid variables between groups.
3. RESULTS

Demographic information for participants is presented in Table 1. Average eGFR was calculated for the experimental group and was 46.83 mL/min/1.73 m² (SD=21.78, range 15.40-83.40) and the control and was 43.45 mL/min/1.73 m² (SD=23.01, range 13.70-90.00) and ANOVA revealed they were not significantly different (P=.69). ANOVA revealed no significant pretest differences in age (P=.55), weight (P=.32), waist circumference (P=.15), serum triglycerides (P=.56), total cholesterol (P=.75), HDL (P=.42), LDL (P=.31), total cholesterol/HDL ratio (P=.97), ApoB (P=.74), albumin (P=.99), and CRP (P=.20) between the experimental and control groups. Additionally, no significant differences between the experimental and placebo groups based on the representation of the ethnic groups (P=.70), gender (P=.59), or stage of CKD (P=.50) were found. A sample size of greater than 30 was chosen to ensure a power of greater than 80% based on formulas published by Freedman [16] in which the alpha level is .05 and the average rate of change in lipid values was 20%. The baseline results are presented in Tables 1 and 2.

| Table 1. Baseline Descriptive Statistics for Fish Oil (FO) and Placebo (P) Groups |
|---------------------------------|---------------------------------|------------------|
| Variable                        | FO Group                        | P Group          | p Value |
| --------------------------------|---------------------------------|------------------|---------|
| Sex, n (%)                      | n = 17                          | n = 14           | 0.59    |
| Male                            | 8 (47.1)                        | 8 (57.1)         |         |
| Female                          | 9 (52.9)                        | 6 (42.9)         |         |
| Ethnicity, n (%)                |                                 |                  | 0.70    |
| African-American                | 10 (58.8)                       | 10 (71.4)        |         |
| Caucasian                       | 4 (23.5)                        | 3 (21.4)         |         |
| Hispanic                        | 3 (17.6)                        | 1 (7.1)          |         |
| Stage of CKD                    |                                 |                  | 0.50    |
| 2 (GFR:60–89 mL/min/1.73 m²)    | 5                               | 4                |         |
| 3 (GFR:30–59 mL/min/1.73 m²)    | 7                               | 4                |         |
| 4 (GFR:15–29 mL/min/1.73 m²)    | 5                               | 5                |         |
| 5 (GFR <15 mL/min/1.73 m²)      | 0                               | 1                |         |
| Age, y±SD                       | 64±10                           | 62±10            | 0.55    |
| Weight (kgs)                    | 98.43±24.04                     | 107.96±30.39     | 0.32    |
| Waist (in)                      | 43.01±6.21                      | 47.59±10.85      | 0.15    |
| Albumin (mg/dL)                 | 4.11±0.34                       | 4.11±0.39        | 0.99    |
| CRP (mg/dL)                     | 0.55±0.35                       | 0.85±0.83        | 0.20    |
| Diabetes Diagnosis, n (%)       | 10 (58)                         | 7 (50)           | 0.56    |

ANOVA revealed a significant difference at posttest (P=.02; Cohen’s d=-0.58), with HDL. No significant differences at posttest were discovered for triglycerides (P=.66; Cohen’s d=0.16), total cholesterol (P=.84; Cohen’s d=0.04), LDL (P=.39; Cohen’s d=0.25), total cholesterol/HDL ratio (P=.34; Cohen’s d=0.20), and ApoB (P=.52; Cohen’s d=0.11). The average compliance rate was calculated to be 82%, with a range from 43% to 100%. Six patients in the fish oil group and five patients in the control groups were considered non-compliant. Pretest and Posttest cholesterol results are presented in Table 2.
Table 2. Differences between fish oil (FO) and placebo (P) groups

| Variable                  | FO group          | P group          | p value** | Cohen’s d |
|---------------------------|-------------------|------------------|-----------|-----------|
| Pretest Triglycerides (mg/dL) | 144.24±93.74      | 126.14±73.50     | 0.56      | 0.16      |
| Posttest Triglycerides (mg/dL) | 146.53±121.92     | 165.21±104.16    | 0.66      |           |
| Pretest Total Cholesterol (mg/dL) | 167.41±36.80     | 172.00±41.06     | 0.75      |           |
| Posttest Total Cholesterol (mg/dL) | 180.24±40.34     | 178.36±46.20     | 0.84      | -0.04     |
| Pretest HDL (mg/dL) | 38.47±14.18       | 35.07±6.98       | 0.42      |           |
| Posttest HDL (mg/dL)* | 43.94±15.08       | 36.64±9.27       | 0.02      | -0.58     |
| Pretest LDL | 100.11±30.00      | 111.86±33.54     | 0.31      |           |
| Posttest LDL (mg/dL) | 103.56±26.24      | 111.85±39.25     | 0.39      | 0.25      |
| Pretest Total Cholesterol/HDL Ratio | 5.14±2.78        | 5.11±1.78        | 0.97      |           |
| Posttest Total Cholesterol/HDL Ratio | 4.67±2.35        | 5.06±1.50        | 0.34      | 0.20      |
| Pretest ApoB (mg/dL) | 87.41±27.58       | 90.43±21.79      | 0.74      |           |
| Posttest ApoB (mg/dL) | 90.29±22.74       | 93.00±25.70      | 0.52      | 0.11      |

* Significantly different
** Posttest results are from ANCOVA with known covariates of body mass, waist circumference, albumin, CRP, and dietary supplement compliance

4. DISCUSSION

In a comprehensive review of published studies encompassing a variety of patient populations (utilizing placebo-controlled studies lasting ≥ 2 weeks and where < 7 g/day of fish oil was consumed), it was concluded that triglyceride concentrations decreased by 25-30%, LDL concentrations increased by 5-10%, and HDL concentrations increased by 1-3%, but total cholesterol was not significantly affected [17]. To date, several randomized and placebo-controlled studies have also investigated the effects of fish oil consumption on various lipid variables in ESRD patients receiving [9,10,12,18-20] and not receiving chronic hemodialysis [2]. However, randomized and placebo-controlled research examining the effects of non-prescription fish oil supplementation on lipid variables in non-hemodialysis patients is limited with few studies to date. As a result, we investigated the effects of an over-the-counter fish oil supplement on various lipid variables in non-dialysis CKD patients.

Our study revealed that levels of HDL were significantly different (with a modest effect size: Cohen’s D=0.58), between the fish oil and placebo groups after 8 weeks of supplementation. Specifically, the group that consumed the fish oil led to a 15.8% increase in HDL. Percent change was calculated using (post test value – pre-test value) / pre-test value)*100. No significant differences were noted in LDL, total cholesterol, total cholesterol/HDL ratio, triglycerides, or ApoB between fish oil and placebo groups at either baseline or posttest.

Research examining ESRD patients have reported both increases [2,10] and decreases [12] in HDL (ranging from -9.3 to + 40.2% change) when 1.3-2.4 g/d of combined EPA and DHA [2,10,12] were consumed for 8-24 weeks. Additionally, Khajehdehi et al. [9] reported increases in serum HDL by 138% (baseline HDL=0.83 mmol/L; post intervention HDL=1.98
mmol/L) following the administration of 1.5 g/day of fish oil (no information was provided on the breakdown of DHA and EPA) over 2 months in hemodialysis patients. It should be noted, however, that these results [9] are markedly higher than other studies of similar design. In our study, the individuals in the fish-oil group consumed 1400 mg of EPA and 1000mg of DHA per day for eight weeks. The dosages of DHA and EPA in our study, and ultimately the improvements in HDL levels, are similar to the findings of an earlier study by Svensson et al. [12] in which HDL increased by 14.3% when participants consumed 2.4 g/d of n-3 over 8-weeks. Increases in HDL are challenging with CKD patients suggesting fish oil that contains DHA and EPA may offer a novel treatment for these patients. Reasons our study did not agree with previous findings that did not report any changes in HDL may be due to a dose-response relationship, differing lengths of studies, and the study population [21]. Study authors [21] reported increases in HDL-2 with no corresponding increases in HDL suggesting researchers may have only measured HDL levels and failed to measure subfractions of HDL that may be more susceptible to changes when exposed to DHA and EPA. Reasons for increases in HDL in our study may be through the control of cholesterol synthesis and the enhancement of activity associated with the enzyme lipoprotein lipase affecting the transfer of lipids between lipoproteins. Specifically the transfer of lipids may be affected by the reduction in the exchange between lipids in HDL and very-low density lipoproteins (VLDL) [22] by reducing specific cholesteryl ester-exchange. It should be noted that when using the recommended guidelines from the National Cholesterol Education Program (NCEP), the group that consumed the fish oil in the present study increased their HDL levels above the critical threshold of 40 mg/dl making our findings clinically significant as well. Conversely, the placebo group remained below this critical value.

Studies examining the effects of fish oil on LDL in CKD patients are also varied with some showing improvement [9] while others reporting slight increases in LDL [2,10,12]. Our study led to minor increases in LDL levels in the fish oil group (4% increases) that was not statistically significant, with virtually no change in the placebo group. Our results, utilizing less severe CKD patients, are similar to those observed in several previously published papers in which the LDL values in ESRD patients were minimally affected via n-3 consumption [2,10,12]. Most of the reasons for equivocal findings regarding LDL are primarily are due to the dose of DHA and EPA supplemented and the study population. The use of DHA and EPA may be more effective in disease states that have increased levels of cholesterol and inflammation and may be less effective in controlling LDL in CKD patients that have less comorbid conditions than ESRD patients.

Regarding total cholesterol, the individuals in the fish oil group and placebo groups showed slight increases of 7.8% and 3.4%, respectfully. However, we observed no significant differences in total cholesterol between groups either before or after the 8-week intervention. The findings of our investigation yielded similar results to previous studies in CKD patients both receiving [12] and not receiving dialysis [2]. In all of the studies of interest [2,12,23], no significant changes in total cholesterol following chronic fish oil consumption were observed. Finally, though no significant differences were discovered between groups regarding LDL and total cholesterol, both the placebo and fish oil group’s LDL and total cholesterol levels were below the NCEP recommended 130 mg/dl and 200 mg/dl values, respectively. This may help support the hypothesis that fish oil supplements may be more effective in populations whose cholesterol values may be considered high.

Along with reduced HDL, hypertriglycerideremia is common among CKD patients [24,26]. In general, as glomerular filtration rate declines, triglycerides increase and HDL decreases [25]. However, several studies in ESRD populations have shown significant decreases in
triglycerides (11%-38%) following 4-8 weeks of chronic fish oil consumption [2,9,23]. Saifullah et al. [12] also reported a decrease in triglycerides (statistical trend) in hemodialysis patients that consumed 1.3 g of combined EPA and DHA per day for 12 weeks. Equally important, Bowden et al. [10] also reported a 12.9% decrease in serum triglyceride following a much longer intervention of 6 months of fish oil (1.56 g/d of combined EPA and DHA) consumption. Interestingly, in our study, the individuals in the fish oil group actually consumed greater than or equal amounts of combined n-3 than the aforementioned studies [2,9,10,12], but triglycerides remained virtually unchanged. It should be noted our study was of short duration when compared to other studies and there may not have been sufficient time to observe changes in triglycerides.

It has been suggested that elevated ApoB is a risk factor for cardiovascular disease in the general population [27-31]. Furthermore, Muntner et al. [30] reported that after adjusting for age, sex, and race/ethnicity, individuals that had lower levels of estimated glomerular filtration rates (GFR) tended to have progressively higher levels of serum ApoB. More recently, Okubo et al. [32] also demonstrated that individuals with renal dysfunction have elevated levels of ApoB (i.e., apoB-48). The authors suggest that increased ApoB may specifically lead to an increased risk of atherosclerosis and coronary artery disease in CKD patients [32]. However, there is limited research examining the effects of fish oil consumption on ApoB in CKD patients. Our study revealed that ApoB increased slightly by 3 % in both the fish oil and placebo groups at the conclusion of the 8-week study. However, there were no significant differences between groups at either baseline or after post-test. These findings are similar to those of Svensson et al. [2] in which a similar amount of combined EPA and DHA were administered over a comparable time frame that led to non significant increases (4.8%) in ApoB. Conversely, an earlier study by Azar and colleagues [23], reported that when 6 g/day of fish oil (containing 1 g/day of EPA and 0.65 g/day of DHA) was consumed for 4 weeks in hemodialysis patients, ApoB significantly decreased by 17.6%. However, the participants in the study by Azar et al. [23] had markedly higher mean baseline ApoB (182 mg/dl) levels than the individuals in fish oil group in our study and consumed more fish oil during their study. Thus, the significant decrease observed in that study, may be in part, attributable to either the higher dosage of fish oil and/or the higher baseline values of ApoB.

The findings of increased levels of HDL in the fish oil group are significant, but a few limitations occurred in our study. It should be noted that compliance with treatment protocols is complicated by patients with low levels of education and low socio-economic status as evidenced in other studies and make conducting research in this group challenging [33]. Also, the family medicine clinic where the data was collected has a significant problem with patient compliance. Additionally, the sample size was relatively small.

5. CONCLUSIONS

It has been reported that CKD patients will often die of cardiovascular disease before dialysis is warranted [26]. As a result, one or more lipid lowering drugs are often prescribed in this population. However, non-pharmacological interventions that can potentially mitigate the effects of lipids are warranted. Including all of the possible therapeutic interventions, fish oil may be efficacious in CKD patients because these patients typically have low dietary intake of n-3 and often have other co-morbidities that may also be improved through fish oil consumption [8]. To date, there is no consensus on the optimal dosing of n-3 PUFA in CKD patients [8], however, the results of our study suggest the consumption of 2.4 grams of combined EPA and DHA may be an effective nutritional intervention to increase HDL in non-dialysis CKD patients. Finally, the reasons for non-significant findings in all other cholesterol
variables may be due to a dose-response relationship, the short duration of the study, the study population, or the supplements may have simply not worked.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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AUTHOR DISCLOSURE STATEMENT

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