

Effect of Over-the-Counter Fish-Oil Administration on Plasma Lp(a) Levels in an End-Stage Renal Disease Population

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Objective: This study sought to examine the effect of n-3 supplementation on lipoprotein(a) (Lp(a)) levels in end-stage renal disease (ESRD) patients undergoing chronic hemodialysis.

Design: The present study was conducted using a double-blind, permuted-randomized, controlled experimental protocol.

Setting: This study took place at the Central Texas Nephrology Associates Dialysis Clinic (Waco, TX).

Patients: Patients with ESRD and associated with the Central Texas Nephrology Associates who were undergoing chronic hemodialysis participated in this study.

Intervention: Patients with ESRD were followed prospectively while receiving supplements of fish oil (treatment, eicosapentaenoic acid, 0.96 g/day, and docosahexaenoic acid, 0.6 g/day) or corn oil (control subjects) for 6 months. After a 12-hour fast, participants donated 12 mL of blood for analysis of Lp(a) at baseline and at 6 months.

Main Outcome Measure: The comparison of Lp(a) concentration by group at 6 months was the primary outcome measure of the study.

Results: Our study suggests that fish-oil supplementation did not decrease levels of Lp(a) ($P = .66$), compared with control subjects.

Conclusion: We failed to show a significant effect of 6 months of over-the-counter fish-oil supplementation on Lp(a) status in an ESRD population, although results from this study support findings from other studies suggesting that African Americans have higher Lp(a) concentrations than persons of Caucasian descent.

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CARDIOVASCULAR DISEASE (CVD) is a major cause of morbidity and mortality in patients with renal failure.¹ In addition to

many of the established risk factors for CVD in the general population, end-stage renal disease (ESRD) patients also present with uremic dyslipidemia, including elevations in lipoprotein(a) (Lp(a)) and decreased high-density lipoprotein (HDL) levels.^{2,3} Lipoprotein(a) levels were significantly correlated with coronary artery disease in numerous studies,⁴⁻⁶ and according to the National Cholesterol Education Program Adult Treatment Panel III guidelines, Lp(a) is considered an emerging risk factor for coronary heart disease.⁷

Although structurally similar to low-density lipoprotein (LDL), Lp(a) contains an additional molecule of apolipoprotein(a) (apo(a)) linked to apo B-100 through disulfide bonds.⁸ In support of a proatherogenic role, Lp(a) was shown to be

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1051-2276/09/1906-0002\$36.00/0

doi:10.1053/j.jrn.2009.06.005

retained more avidly than LDL in the vessel wall.^{9–11} Further, because the structure of apo(a) resembles that of plasminogen, there is speculation that Lp(a) may interfere with the fibrinolytic system.¹²

Although Lp(a) levels are subject to strong genetic regulation,¹³ some evidence suggests that dietary manipulation may aid in its reduction. Specifically, medicinal levels of niacin have proven effective in Lp(a) level reduction,¹⁴ and epidemiologic evidence supports the notion that diets high in fish may reduce Lp(a) levels.¹⁵ At present, the mechanisms linking high fish intake and lower Lp(a) levels in plasma are unclear. However, n-3 polyunsaturated fatty acids (PUFAs) are speculated to be the active ingredient. It was suggested that n-3 fatty acids directly enter the portal vein system and lower the rate of apo(a) synthesis and/or secretion from the liver.¹⁶ In addition, high levels of n-3 fatty acids were hypothesized to result in impaired assembly of apo(a) with LDL or in enhanced catabolism.¹⁷

At present, there are conflicting results from prospective studies regarding the effect of fish-oil supplementation on Lp(a),^{18–20} and only one randomized, controlled trial has explored this relationship in an ESRD population.²¹ Therefore, because of elevations in this uremic-specific risk factor in the ESRD population and the potential for therapeutic dietary intervention, this study sought to evaluate the ability of fish-oil supplementation to decrease circulating levels of plasma Lp(a) in an ESRD patient population.

Methods

Study Population

The ESRD patients associated with the Central Texas Nephrology Associates who were undergoing chronic hemodialysis participated in this study. Exclusion criteria for this study included a life expectancy of less than 6 months (based on physician prognosis), pregnancy, a history of hemodialysis noncompliance, previous medication noncompliance, no desire to participate in the study, or age of less than 18 years. One-hundred patients 18 years of age and older with a history of dialysis and medication compliance were identified, and 40 patients agreed to participate. Five participants from the control group (omega-6 fatty acids, or n-6) and two participants from the n-3 group did not comply with the supplement protocol and were excluded from the final analysis, for a total sample size

of 33 at study completion. However, all noncompliant participants were encouraged to continue supplementation for the duration of the study, in compliance with the Declaration of Helsinki and “intent to treat” guidelines. There were no participant reports of CVD-related symptoms, and specifically, no findings of palpitations, syncope, clinically significant episodes of arrhythmia, or other cardiac manifestations during the study. Patients meeting eligibility criteria were informed of the requirements of the study and signed informed-consent statements, in compliance with the human-subjects guidelines of the university and clinics for the protection of human subjects in research before the intervention.

Experimental Design and Procedures

The study was conducted using a double-blind, permuted-block, randomized, and controlled experimental design, with a four-block permuted randomization procedure. Each “block” had an equal number of experimental and control group selections (two each), with the order of blocks permuted. Microsoft Excel was used to generate the random number used to assign blocks and randomize group selection. Participants were randomly placed into the n-3 fatty acid (experimental, $n = 18$) or control ($n = 15$) group. Participants in the experimental group consumed two 1-g soft-gel capsules of over-the-counter (OTC) fish-oil concentrate with each meal, or 6 g (six capsules) per 24 hours containing 160 mg of eicosapentaenoic acid (EPA; 0.96 g/day) and 100 mg of docosahexaenoic acid (DHA; 0.6 g/day). The control group consumed two 1-g soft-gel capsules of corn oil with each meal, to accumulate 6 g (six capsules) per 24 hours. Both groups were instructed to take the supplement in the same way. Outcome variables were measured at baseline and at 6 months. Furthermore, all patients consumed vitamin supplements that contained 15 mg of B₆, 12 mg of B₁₂, and 2.5 mg of folic acid.

Supplement Distribution and Compliance

Participants’ regular renal dietitians distributed study materials and monitored supplement and dietary compliance. Dietitians issued a 1-month supply six times during the study period for each patient. Moreover, the dietitian and clinic

physician consulted with the patients three times per week during dialysis sessions throughout the study period. Participants were considered compliant if they consumed 90% of the n-3 fatty-acid soft-gel supplements provided, based on the common practice of “pill-counting.”^{22,23} The renal dietician was responsible for monitoring compliance with all patients.

Dialysis Protocol

The dialysis clinics used polysulfone membranes, with 95% using a Fresenius-160 dialyzer, and 5% using a Fresenius-180 dialyzer (Fresenius Medical Care, Ogden, Utah), at a dialysate flow rate of 800 cm³/minute and a mean blood flow rate of 376.49 cm³/minute. The dialysis dose for both n-3 fatty-acid and control-oil groups entailed a Kt/V range of 1.1 to 2.0, with means of 1.35 and 1.38, respectively. All patients ran 4-hour dialysis duration per unit protocol.

Lipid Analysis

Venous blood samples were collected at baseline and after completion of the supplement intervention 6 months later. A phlebotomist collected approximately 20 mL of blood from each participant (after fasting for 12 hours), using standardized venipuncture techniques in the antecubital vein. Venous samples, intended for serum analysis, were centrifuged and immediately placed in a cold-storage unit and sent for assay. Lipid profiles were assessed using gel electrophoresis with whole-blood samples sent to Quest Diagnostics (Dallas, TX). The Lp(a) was obtained and is reported in micromoles per liter ($\mu\text{mol/L}$), as well as milligrams per deciliter (mg/dL).

Fish-Oil and Control Composition

Fish oil and corn oil (control) were quality-assured and quality-controlled by Royal Numico Research B.V. (Greenville, SC). Fish-oil soft gels were packaged in a 1-g capsule that contained 160 mg of EPA and 100 mg of DHA, and 0.9 IU of d- α tocopherol as an antioxidant. The control soft gels were packaged in a 1-g capsule of corn oil (94% unsaturated fat, 6% saturated fat). The fish-oil and corn-oil supplements were indistinguishable from each other, and were “minted” to have the same flavor. Patients, physicians, and researchers were blinded to which supplement patients were consuming. Corn oil was used as

a control in a number of studies associated with n-3 supplementation and lipid changes.^{24–27}

Statistical Analysis

We summarized all baseline demographic information using frequencies and percentages for categorical variables, and means and standard deviations for continuous variables. We assessed the primary research question of whether the fish-oil intervention had a different effect on Lp(a) concentrations compared with the control, by using a repeated-measures analysis of variance (ANOVA) and testing for significance the multivariate Wilks' λ statistic for the group-by-time interaction. This allows for appropriate control of within-individual variability of the data, while ascertaining whether there is a difference in Lp(a) response over time as a result of the intervention. Of secondary interest, if the first test did not produce significant results, was the issue of whether a time effect or group effect existed within the data.

A secondary aim of the study was to explore the qualities that affect Lp(a) levels, given the findings of the first portion of the study. We used three repeated-measures ANOVA models with age, race, and gender as predictors. This necessitated removing the three Hispanic individuals from the data, because the available sample size was inadequate for a subgroup analysis. The use of three separate models was necessary, given that the sample size of the study could not sustain a model with all covariates and interactions. All data summaries and statistical results were produced using SAS, version 9.2 (SAS Institute, Cary, NC). We performed all comparisons using a type I error rate of 0.05.

Results

A full summary of baseline characteristics of the study groups is presented in Table 1. There were no statistically significant post-randomization differences between groups at baseline for any variable, which we interpret as lending balance to the two groups. Table 2 contains the primary results of the study, i.e., whether supplementation had an effect on Lp(a) values over the course of the study. The nonsignificant interaction test indicates no significant difference in the effect of either fish or corn oil on Lp(a) values. Furthermore, no overall group differences exist, and the effect of time was marginally nonsignificant. Given that the

Table 1. Participant Demographics and Baseline Lp(a) Levels

	Fish Oil	Corn Oil	P Value
n	18 (55)	15 (45)	
Male	7 (39)	7 (47)	.66
Age (y)	57 (13)	64 (14)	.14
Race			.87
White	6 (33)	6 (40)	
African American	10 (56)	8 (53)	
Hispanic	2 (11)	1 (7)	
Months on dialysis	36 (28)	21 (12)	.08
Presence of diabetes	13 (72)	7 (47)	.14
Current smoker	3 (17)	5 (33)	.27
Lp(a) in $\mu\text{mol/L}$	1.29 (1.14)	1.14 (0.86)	.66
Lp(a) in mg/dL	36 (32)	32 (24)	.66

No significant differences were evident at baseline. Discrete variables are presented as frequencies (%), whereas continuous variables are presented as means (standard deviations).

means of both groups decreased over the intervention period, this could indicate a downward Lp(a) trend as a result of treatment with either oil group.

The results of the secondary study endpoint, to evaluate whether age, gender, or race are significantly associated with Lp(a) values, are contained in Table 3. There were no significant differences among gender groups, although this may be partly attributable to the high variability within each group. The observed data means were substantially lower for males at each time point, but the large data variability obfuscated this relationship. Because of the large data variability, we performed a nonparametric analysis of the data that yielded no differences in the results. Furthermore, there does not appear to be a significant relationship between age and Lp(a) values at either time point.

The relationship between race and Lp(a) concentrations indicate a significant difference across racial groups, independent of the time point of the intervention. African Americans tended to exhibit significantly higher values of Lp(a) compared with whites, and the nonsignificant interaction indicates that neither group changed significantly from baseline as a result of the intervention.

Discussion

Based on recent reports from the United States Renal Data System, the prevalence of coronary heart disease (CHD) in hemodialysis (HD) patients is 40%, and the CVD mortality in this group is up to 30 times higher than in the general population.²⁸ As such, the identification of effective strategies to attenuate the progression of CVD in this demographic is warranted. In persons undergoing HD, the consumption of appreciable amounts of n-3 PUFA was shown to produce beneficial effects on varied cardiovascular indices, including lipids, platelets, and blood pressure,²⁹ and recent research led to the speculation that it might also lower levels of Lp(a).

In the present investigation, we failed to show a significant effect of 6 months of OTC fish-oil supplementation on Lp(a) status in an ESRD population, although results from this study support findings from other studies suggesting that African Americans have higher Lp(a) concentrations than persons of Caucasian decent.³⁰ Although some studies suggest that fish-oil supplementation can mediate Lp(a) expression,^{18,19} our findings concur with a study of a similar design by Svensson et al.²¹ In that double-blind controlled trial, 206 HD patients were randomized to consume either 1.7 g/day of n-3 fatty acid (EPA, 45%; DHA, 37.5%) or olive-oil capsules for 3 months. Participants were evaluated at a clinical examination and via blood sampling at baseline and after 3 months of treatment. Although the results of the trial suggest that n-3 PUFA supplementation lowers serum triglycerides, fish-oil supplementation was not shown to significantly affect other plasma lipids or lipoproteins, including Lp(a).

Given the inconsistencies in the literature, it is of interest to determine why some studies support the effectiveness of a fish-oil dietary intervention to lower Lp(a), and others do not. After reviewing the relevant study designs, we believe such inconsistencies may be explained by different treatment durations, n-3 PUFA dosages, patient populations

Table 2. Results of Repeated-Measures ANOVA by Group

	Fish-Oil Group, $\mu\text{mol/L}$ (mg/dL)	Corn-Oil Group, $\mu\text{mol/L}$ (mg/dL)	Test	P Value
Lp(a) at baseline	1.29 \pm 1.14 (36 \pm 32)	1.14 \pm 0.86 (32 \pm 24)	Group * Time	.66
Lp(a) after intervention	1.14 \pm 1.29 (32 \pm 36)	0.86 \pm 0.54 (24 \pm 15)	Group	.52
			Time	.09

Data are expressed as means \pm standard deviations.

Table 3. Analysis of Changes in Lp(a) by Important Confounders

Variable	Test for Significance	P Value
Age	Age	.81
	Time	.12
	Age * Time	.22
Race*	Race	.03
	Time	.11
	Race * Time	.9
Sex	Sex	.2
	Time	.11
	Sex * Time	.6

*Hispanic subjects were omitted because of small sample size (n = 3).

assessed, and biological variability in Lp(a) measurement.

By far, the most compelling support for the a Lp(a)-lowering effect of fish oil is epidemiologic in nature. The genetically controlled population-based study of Marcinova et al.¹⁵ provides the most persuasive evidence that the dietary content of n-3 PUFA can interfere with the expression of Lp(a). Those authors assessed the Lp(a) levels of two Bantu populations of Tanzania, one living on freshwater fish (n = 622), and the other living on a mainly vegetarian diet (n = 686).¹⁵ These populations were selected because they are largely genetically and environmentally homogeneous, with the exception of dietary intake. As such, the researchers hypothesized that any observed disparities in Lp(a) levels must be due to differences in diet. When plasma Lp(a) levels were assessed, a 48% difference was found between groups (0.96 $\mu\text{mol/L}$ [27 mg/dL] in the vegetarian population, and 0.50 $\mu\text{mol/L}$ [14 mg/dL] in the fish-diet population; $P < .0001$). Further, to control for the variability in apo(a) size known to influence Lp(a) levels, a subset of the population was selected (n = 410 per village) and matched for apo(a) phenotypes. In doing so, median Lp(a) values were still found to be 40% lower in the fishermen than in the reference population. This elegantly designed study, which attempted to control for genetic variation in Lp(a) levels, strongly suggests that diets high in fish (and the associated fish oil) can be effective in lowering Lp(a) levels.

Unlike the Bantu population that subsisted on a primarily fish-based diet, participants in our study were under no such dietary control. Moreover, it may not be realistic to presume that the results of a randomized, controlled trial

assessing 6 months of OTC fish-oil consumption would be comparable in dose or duration to a lifetime of fish intake.

Moreover, compared with clinical trials that showed the Lp(a)-lowering effect of fish oil,^{18,19} our study used comparable amounts of n-3 PUFA (1.57 to 4.5 g/day) for a longer period of time (6 to 12 weeks), but the patient populations significantly differed. Specifically, those studies looked at healthy volunteers and persons with elevated triglycerides, whereas our study examined a chronically ill patient population. Among other risk factors, Lp(a) levels are significantly elevated in ESRD patients.³¹ Therefore, it is reasonable to speculate that the plasma level of Lp(a) may have been elevated for a prolonged period of time, and to such an extent that dietary supplementation occurred too late in the morbid condition to produce beneficial results.

A rather interesting and unexpected finding of this study is a trend of decreasing Lp(a) emerging in the corn-oil (control) group. Corn oil has been used routinely as a control oil in lipid studies,²⁴⁻²⁷ but limited evidence, published after our data were collected, suggests a beneficial effect of corn oil on lipids and Lp(a).³² Willett³² suggested in a review that n-6 fatty acids may play a role in reducing the rate of CVD, specifically through the reduction of lipid levels and Lp(a). However, a review of the literature of n-6 as a treatment oil for elevated lipids in ESRD patients revealed only one related study.³³ Khajehdehi³³ reported decreased LDL and increased HDL in ESRD patients who supplemented 4.5 g of corn oil for 2 months, but did not report Lp(a) changes. Therefore, the effect of corn oil on lipid levels in the HD population remains to be well-elucidated, and this finding should be reported with caution.

Limitations

A few limitations of the study design are worth noting. First, compliance to the dietary protocol in our study was assessed using the standard method of pill-counting. Although good compliance was reported in all participants retained for analysis (>90%), future studies should use more objective measures, such as in vivo testing to confirm patient compliance. Second, although supplements were quality-controlled and quality-assured by the manufacturer before shipping, OTC supplements can have significant variation in content.

Therefore, the amounts of DHA and EPA per capsule may have varied, thereby decreasing the likelihood of detecting a significant difference in Lp(a) concentration. Third, in terms of assessing cardiovascular risk, the way in which Lp(a) was measured in our study, although widely practiced, ignores the variation in apo(a) gene size when quantifying Lp(a) levels. Several studies showed that Lp(a) particles that carry small apo(a) molecules are associated with increased cardiovascular risk,^{34,35} especially in ESRD patients,³⁶ and therefore may provide limited information on true cardiovascular risk. Lastly, the large intra-individual variability of our dataset may have limited our ability to observe a significant effect of fish oil on Lp(a). Values of Lp(a) in our dataset ranged from 0.02 to 3.26 $\mu\text{mol/L}$ (0.6 to 91.3 mg/dL) at baseline, and 0.02 to 3.81 $\mu\text{mol/L}$ (0.5 to 106.9 mg/dL) after supplementation, with intra-individual before-and-after differences from -2.40 to 0.92 $\mu\text{mol/L}$ (-67.1 to 25.8 mg/dL). However, given the current assessment technology, such variability may be common. Marcovina et al. showed that the biological variability for Lp(a) is high, ranging anywhere from 1% to 51%, depending on Lp(a) concentration.³⁷ Future research should focus on the nature of the variability of Lp(a), i.e., whether such variability is largely biological in nature, or reflects a flaw in the measurement process. In the present study, a larger sample size could have overcome the loss in power due to the sizable variability of data.

Conclusions

Levels of Lp(a) are poorly understood and seldom studied in ESRD patients. Our study followed patients prospectively for 6 months while supplementing fish oil in their diet, using an OTC product. The results of our study suggest that fish-oil supplementation did not decrease levels of Lp(a). Yet, as evidenced by trends in our fish-oil and corn-oil groups, further study is warranted for both n-3 and n-6 fatty acids. Furthermore, researchers demonstrated a positive effect on other lipids after n-3 supplementation, suggesting the need for further study.

Acknowledgments

Data were collected in clinics associated with the Central Texas Nephrology Associates. Partial funding was provided by the University Research Committee of Baylor University

(Waco, TX). Fish-oil and corn-oil supplements were provided by Royal Numico (Wageningen, The Netherlands).

References

1. Excerpts from the United States renal data system 1998 annual data report. *Am J Kidney Dis* 32(Suppl):S1-S162, 1998
2. Longenecker JC, Coresh J, Powe NR, et al: Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol* 13:1918-1927, 2002
3. Shoji T, Kimoto E, Yamada A, et al: Elevated plasma free apo(a) levels in hemodialysis patients. *Nephron* 83:389-390, 2000
4. Rhoads GG, Dahlen G, Berg K, et al: Lp(a) lipoprotein as a risk factor for myocardial infarction. *JAMA* 256:2540-2544, 1986
5. Bostom AG, Gagnon DR, Cupples LA, et al: A prospective investigation of elevated lipoprotein (a) detected by electrophoresis and cardiovascular disease in women. The Framingham Heart Study. *Circulation* 90:1688-1695, 1994
6. Wild SH, Fortmann SP, Marcovina SM: A prospective case-control study of lipoprotein(a) levels and apo(a) size and risk of coronary heart disease in Stanford Five-City Project participants. *Arterioscler Thromb Vasc Biol* 17:239-245, 1997
7. National Institutes of Health. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486-2497, 2001
8. Huby T, Schroder W, Doucet C, et al: Characterization of the N-terminal and C-terminal domains of human apolipoprotein(a): relevance to fibrin binding. *Biochemistry* 34:7385-7393, 1995
9. Beisiegel U, Niendorf A, Wolf K, et al: Lipoprotein(a) in the arterial wall. *Eur Heart J* 11:174-183, 1990
10. Dangas G, Mehran R, Harpel PC, et al: Lipoprotein(a) and inflammation in human coronary atheroma: association with the severity of clinical presentation. *J Am Coll Cardiol* 32:2035-2042, 1998
11. Nielsen LB: Atherogenicity of lipoprotein(a) and oxidized low density lipoprotein: insight from in vivo studies of arterial wall influx, degradation and efflux. *Atherosclerosis* 143:229-243, 1999
12. Miles LA, Plow EF: Lp(a): an interloper into the fibrinolytic system? *Thromb Haemost* 63:331-335, 1990
13. Utermann G: The mysteries of lipoprotein(a). *Science* 246:904-910, 1989
14. Carlson LA, Hamsten A, Asplund A: Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. *J Intern Med* 226:271-276, 1989
15. Marcovina SM, Kennedy H, Bittolo Bon G, et al: Fish intake, independent of apo(a) size, accounts for lower plasma lipoprotein(a) levels in Bantu fishermen of Tanzania: the Lugalawa Study. *Arterioscler Thromb Vasc Biol* 19:1250-1256, 1999
16. Nelson GJ, Ackman RG: Absorption and transport of fat in mammals with emphasis on n-3 polyunsaturated fatty acids. *Lipids* 23:1005-1014, 1988
17. Herrmann W, Biermann J, Kostner GM: Comparison of effects of n-3 to n-6 fatty acids on serum level of lipoprotein(a) in patients with coronary artery disease. *Am J Cardiol* 76:459-462, 1995
18. Haglund O, Mehta JL, Saldeen T: Effects of fish oil on some parameters of fibrinolysis and lipoprotein(a) in healthy subjects. *Am J Cardiol* 74:189-192, 1994

19. Beil FU, Terres W, Orgass M, et al: Dietary fish oil lowers lipoprotein(a) in primary hypertriglyceridemia. *Atherosclerosis* 90:95-97, 1991
20. Eritsland J, Arnesen H, Berg K, et al: Serum Lp(a) lipoprotein levels in patients with coronary artery disease and the influence of long-term n-3 fatty acid supplementation. *Scand J Clin Lab Invest* 55:295-300, 1995
21. Svensson M, Schmidt EB, Jorgensen KA, et al: The effect of n-3 fatty acids on lipids and lipoproteins in patients treated with chronic haemodialysis: a randomized placebo-controlled intervention study. *Nephrol Dial Transplant* 23:2918-2924, 2008
22. Jasti S, Siega-Riz AM, Cogswell ME, et al: Pill count adherence to prenatal multivitamin/mineral supplement use among low-income women. *J Nutr* 135:1093-1101, 2005
23. Lee JY, Kusek JW, Greene PG, et al: Assessing medication adherence by pill count and electronic monitoring in the African American Study of Kidney Disease and Hypertension (AASK) Pilot Study. *Am J Hypertens* 9:719-725, 1996
24. Grundt H, Nilsen DW, Hetland O, et al: Clinical outcome and atherothrombotic risk profile after prolonged wash-out following long-term treatment with high doses of n-3 PUFAs in patients with an acute myocardial infarction. *Clin Nutr* 23: 491-500, 2004
25. Wu WH, Lu SC, Wang TF, et al: Effects of docosahexaenoic acid supplementation on blood lipids, estrogen metabolism, and in vivo oxidative stress in postmenopausal vegetarian women. *Eur J Clin Nutr* 60:386-392, 2006
26. Helland IB, Saugstad OD, Saarem K, et al: Supplementation of n-3 fatty acids during pregnancy and lactation reduces maternal plasma lipid levels and provides DHA to the infants. *J Matern Fetal Neonatal Med* 19:397-406, 2006
27. Mostad IL, Bjerve KS, Lydersen S, et al: Effects of marine n-3 fatty acid supplementation on lipoprotein subclasses measured by nuclear magnetic resonance in subjects with type II diabetes. *Eur J Clin Nutr* 62:419-429, 2008
28. Harper CR, Jacobson TA: Managing dyslipidemia in chronic kidney disease. *J Am Coll Cardiol* 51:2375-2384, 2008
29. Rylance PB, Gordge MP, Saynor R, et al: Fish oil modifies lipids and reduces platelet aggregability in haemodialysis patients. *Nephron* 43:196-202, 1986
30. Marcovina SM, Albers JJ, Wijnsman E, et al: Differences in Lp[a] concentrations and apo[a] polymorphs between black and white Americans. *J Lipid Res* 37:2569-2585, 1996
31. Barbagallo CM, Aversa MR, Sparacino V, et al: Lipoprotein (a) levels in end-stage renal failure and renal transplantation. *Nephron* 64:560-564, 1993
32. Willett WC: The role of dietary n-6 fatty acids in the prevention of cardiovascular disease. *J Cardiovasc Med* 8(Suppl): S42-S45, 2007
33. Khajehdehi P: Lipid-lowering effect of polyunsaturated fatty acids in hemodialysis patients. *J Ren Nutr* 10:191-195, 2000
34. Sandholzer C, Saha N, Kark JD, et al: Apo(a) isoforms predict risk for coronary heart disease. A study in six populations. *Arterioscler Thromb* 12:1214-1226, 1992
35. Paultre F, Tuck CH, Boden-Albala B, et al: Relation of Apo(a) size to carotid atherosclerosis in an elderly multiethnic population. *Arterioscler Thromb Vasc Biol* 22:141-146, 2002
36. Longenecker JC, Klag MJ, Marcovina SM, et al: Small apolipoprotein(a) size predicts mortality in end-stage renal disease: the CHOICE Study. *Circulation* 106:2812-2818, 2002
37. Marcovina SM, Gaur VP, Albers JJ: Biological variability of cholesterol, triglyceride, low- and high-density lipoprotein cholesterol, lipoprotein(a), and apolipoproteins A-I and B. *Clin Chem* 40:574-578, 1994