Int J Endocrinol Metab 2004; 2:87-94

ORIGINAL ARTICLE

Effects of Purified Omega-3 Fatty Acids on Serum Lipoproteins and Malondialdehyde in Postmenopausal Fat Women Receiving Hormone Replacement Therapy

Shidfar F[a], Keshavarz A[b], Jalali M[a], Miri R[c], Amri A[a], Shidfar SH[d].

[a]School of Health, Iran University of Medical Sciences, [b] School of Public Health, Tehran University of Medical Sciences, [c] Shaheed Beheshti University of Medical Sciences, Tehran, I.R.Iran; [d]Memorial Hospital, University of Massachusetts, Worcester, USA

Regular intake of n-3 fatty acids of marine origin have desirable effects on serum lipoproteins and reduce coronary vascular disease (CVD). n-3 fatty acid supplementation decreased serum triglyceride concentrations in studies in which most of the subjects were male. The effects of n-3 fatty acids supplementation in fat women especially postmenopausal fat women have received little attention. The aim of this study was to determine whether purified n-3 fatty acids have desirable effects on serum lipoproteins, malondialdehyde (MDA) and lipoprotein risk factors for CVD in postmenopausal fat women receiving hormone replacement therapy (HRT).

Materials and Methods: In a double-blind, placebo-controlled trial of parallel design, 35 postmenopausal women receiving hormone replacement therapy were randomly allocated to receive 2 g purified n-3 fatty acids or placebo for 10 weeks. Serum lipoproteins and MDA were determined on days 0 and 70.

Results: Serum levels of triglycerides (TG) decreased significantly in the n-3 fatty acids group at the end of study compared to the initial values, and also compared to control group (26%, p< 0.003 and 29%, p< 0.01, respectively). In the n-3 fatty acids group, serum levels of TG/HDL-C decreased significantly at the end of the study compared to initial values and, at the end of the study, compared to control group as well (23 %, p <0.05 and 28%, p< 0.05)

Conclusion: Supplementation with purified n-3 fatty acids can favorably influence selected CHD risk factors, particulary by achieving marked reduction in serum TG and TG/HDL-C levels in postmenopausal fat women receiving HRT.

Key Words: n-3 fatty acids, Triglycerides, Postmenopausal women, HDL–C, Malondialdehyde

Introduction

Coronary heart disease (CHD) is the most deadly cardiovascular disease, with hyperlipidemia being one of its major risk factors.[1] However, high LDL-Cholesterol (LDL-C) and low HDL cholesterol (HDL-C) concentrations are well-established risk factors for CHD[2], but increase in serum TG concentration is associated with small dense LDL particles and hypercoagulability.[3]

TG:HDL-C ratio has been shown to be a stronger predictor of myocardial infarction

Correspondence: Farzad Shidfar, Department of nutrition, School of Health, Iran University of Medical Sciences, P.O. Box 15875-4199, Tehran, I.R.Iran
E-mail: farzad shidfar@yahoo.com

than either total cholesterol: HDL-C or LDL-C: HDL-C ratio.[2-6] Each 8.8 mg/dL increase in TG is associated with a 1.4% and 3.7% increase in CVD in men and women, respectively.[7] The levels of total cholesterol (TC) and LDL-C are lower in premenopausal women than in men, although they gradually increase with age and after menopause they increase rapidly.[3] Indeed, menopause is associated with a significant increase in CVD risk.[8] It is known that estrogens increase HDL-C and decreases LDL-C. Observational studies have found lower rates of CHD in postmenopausal women receiving exogenous estrogens. It is thought that the decreases in LDL-C and increases in HDL-C that are associated with estrogen use provide protection against CVD.[3,9,10] Recent studies show that hormone replacement therapy (HRT) has no beneficial effect on CVD risk despite improvement in LDL-C and HDL-C concentrations because TG concentrations increases significantly.[4,11,12] Epidemiologic studies have indicated that populations who consume large amounts of n-3 polyunsaturated fatty acid-enriched fish oil have a low incidence of CVD. n-3 fatty acids have a wide range of biological effects, for example, antithrombotic, antiatherogenic, antiarrhythmic and antihypertensive properties.[13-18] n-3 fatty acids decrease VLDL synthesis and secretion, and serum TG, but the effect on LDL-C and malondialdehyde (MDA) (as an index for lipid peroxidation) is controversial.[13-19] In view of the benefical effects of n-3 fatty acids in CHD and the need of postmenopausal women for a suitable food supplement to improve serum lipoproteins, this study was undertaken to investigate the association between the above.

The aim of this study was to determine the effects of n-3 fatty acids supplementation on serum lipoproteins and MDA in postmenopausal fat women receiving HRT.

Materials and Methods

Study population

Nonsmoker postmenopausal women, who had ceased menstruation ⩾ 1 year prior to study initiation and were otherwise healthy, were randomly recruited from Shariati hospital, Tehran, Iran. All the women eligible had experienced natural menopause (i.e. they had not undergone surgical menopause). Inclusion criteria included serum TC and TG concentrations ⩾200 mg/dL, a BMI between 25 and 30, and no recent (the past 3 months) symptomatic heart disease, diabetes, liver or renal disease. All of the women were receiving similar HRT (0.625 mg conjugated estrogen and 2.5 mg medroxyprogesterone acetate daily). None of the subjects took any nonsteroidal antiinflammatory, antihypertensive , or lipid-lowering drugs. The Human Ethics Committee of Tehran University of Medical Sciences approved this study and all subjects gave their written informed consent.

Dietary education and intervention study design

A socio-economic questionnaire was completed for each subject. All of the women were receiving similar HRT. The women were stratified by serum TC and TG before being randomly assigned to one of two groups (Group 1: 2g n-3 fatty acids. Group 2: 2g placebo). Supplementation was continued for ten weeks.

Both the n-3 fatty acids supplement and the placebo were provided as 1-g capsules. n-3 fatty acid capsules contained only purified EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), provided by Advanced Nutritional Technology Co, Super EPA

2000, USA. The placebo contained 300 mg saturated fatty acids, 100 mg mono-unsaturated fatty acids and 600 mg linoleic acid. All participants were instructed to maintain their usual diets, physical activities and lifestyles and to refrain from making any changes throughout the intervention period. The same dietitian monitored the dietary intake of all the patients at the beginning and at the end of fifth and tenth weeks of the study by administering 24-hour dietary recall questionnaires. The patients were followed up by telephone each week; patients who had no phone were instructed to return to the clinic every other week.

Laboratory analyses

Fasting blood samples were collected at the beginning and at the end of the intervention period (10th weeks).

Blood samples were collected after 12h fasting overnight. Serum was obtained by low-speed centrifugation at 1000g at 4°C for 10min, within 1h of venipuncture, transferred to plastic tubes in portions and stored at-80° C until analyzed.

Serum lipoproteins were analyzed with a Cobas MIRA analyzer (Roche Diagnostics, Basel, Switzerland). Total serum cholesterol and TG levels were measured enzymatically with the tricylglycerol GPO-PAP-cholesterol CHOD-PP kit (MAN Co, Iran). Serum HDL-C was determined enzymatically using the CHOD-PAP kit after precipitation of the chylomicrons, VLDL and LDL with phosphotungstic acids and Mg^{2+}. Serum LDL- c was determined enzymatically using the CHOD-PAP kit after precipitation of LDL with heparin and sodium citrates and then by utilizing the following formula: LDL-C=[TC]-[cholesterol] in the supernatant. MDA was measured colorimetrically.[20] The within-assay CV for these assays (n=10) were 1.2, 1.2, 1.1 and 1.3% for TC, 1.2, 1.1 and 1.3% for TC, HDL-C, LDL-C and TG, respectively, and the between-assay CV (n=10) were 0.8, 1.1, 0.9 and 1.5% respectively.

Statistical analysis

Data are expressed as mean±SD. The level of significance chosen was $p < 0.05$. In order to test whether the difference of the mean values of the item studied in both groups were significant, t test was used. Differences in the same hyperlipidemic patients before and after 10 weeks of intervention were evaluated by paired t test. Diet records were analyzed by Food Processor II software. For comparison of means at different intervals of 24-hour recall questionnaires, ANOVA was used. For qualitative variables (e.g. income, occupation, education) a chi-square test was used. Statistical analyses were performed with SPSS (version 10).

Results

35 postmenopausal women completed the study. Baseline characteristics of the two groups confirmed that they were well matched for the inclusion criteria (Tables 1, 3 and 4). Evidence of adherence to the diets came from analysis of diet records and capsule counts. There was no significant difference in body weight between groups at baseline (Table 1) and no significant change during the intervention (Table 2). Analyses of the diet records indicated no significant change during the intervention (Table 2).

Table 1. Characteristics of participants in the 2 groups at baseline

Characteristics	n-3 fatty acids (n=17)	control (n=18)
Age (year)	53.3 (10.1)	54.4 (10.9)
Weight (kg)	73.5 (9.1)	71.9 (8.7)
BMI (kg/m^2)	26.8 (2.1)	27.1 (7.5)

Numbers represent mean (SD).

Table 2. Total energy, fat and fiber intake and weight of participants at baseline and during the intervention in the 2 groups

Variables	Control (n=18)	n-3 fatty acids (n=17)
Total energy intake (kcal/day)		
Baseline	1874 (439)	1810 (361)
5th week	1790 (401)	1788 (508)
10th week	1823 (431)	1791 (453)
Saturated fatty acids (g)		
Baseline	22.0 (2.2)	21.7 (1.8)
5th week	19.5 (1.4)	20.7 (1.9)
10th week	19.9 (1.7)	20.9 (1.7)
Polyunsaturated fatty acids(g)		
Baseline	11.8 (1.0)	10.2 (1.1)
5th week	13.1 (1.1)	12.2 (1.0)
10th week	12.9 (1.2)	13.1 (1.2)
Dietary fibre (g)		
Baseline	20.3 (1.1)	18.4 (2)
5th week	19.9 (1.2)	18.2 (1.7)
10th week	20.1 (1.3)	19.0 (2.4)
Cholesterol (g)		
Baseline	221 (35)	198 (19)
5th week	217 (22)	191 (17)
10th week	224 (31)	201 (36)
Weight (kg)		
Basecline	71.9 (8.7)	73.5 (9.1)
5th week	72.8 (8.3)	74.6 (8.8)
10th week	73.9 (8.1)	75.5 (8.9)
Income	106 (70)	109 (70)
Education (%)		
Illiterate	15	17
Primary school	35	33
High school diploma and higher	55	60
Occupation (%)		
Housekeeper	55	59
Employee	45	41

Numbers represent mean (SD).
* Average monthly family income

There was no significant difference between women receiving HRT regarding duration of treatment. There were no significant differences in fasting serum lipoproteins and MDA at baseline between the groups (Tables 3, and 4). There was a significant difference in serum TG at the end of study as compared to the initial value in the n-3 fatty acids group ($p< 0.003$), and also to the final value in the control group ($p<0.01$). At the end of the study in the n-3 fatty acids group, the TG/HDL-C had significantly decreased compared to that at the beginning ($p<0.05$), and also compared to control group ($p<0.05$). There were no significant changes in LDL-C TC, MDA and HDL-C during the 10 weeks of study. Tables 3 and 4 show the serum lipoproteins and MDA of postmenopausal women at baseline and after the intervention in the two groups.

Discussion

This randomized, double blind, placebo-controlled trial of parallel design assessed whether or not purified n-3 fatty acids have favorable effects on serum lipoproteins, and MDA in postmenopausal women. We found that purified n-3 fatty acids significantly decreased serum TG and TG/HDL-C concentrations, without affecting other lipoproteins variables that we measured. At the end of the study, a significant decrease was seen in serum TG in the n-3 fatty acids group as compared to initial value and also compared to the control value, which was consistent with previous studies.[9-12]

The primary action of n-3 fatty acids is believed to be facilitating lipoprotein lipase-mediated lipolysis, decreased hepatic synthesis of TG and decreased VLDL and TG secretion.[4,13,15,16,18,21,22] Previous studies indicated that n-3 fatty acids decrease TG by 25-30% in normolipidemic subjects.[7] In the present study, n-3 fatty acids decreased serum TG by 26 % in postmenopausal women, a reduction which could decrease CVD risk by a predicted 27% in postmenopausal women.[7] Previous studies showed serum TG reductions of 30% in women not receiving HRT,[19] decreases of 28%,[19] 8%[10] and 27%[3] in women receiving HRT. Lox et al reported that fish oil consumption by healthy women of reproductive age, not receiving HRT, should be avoided (due to high increase in

Table 3. Fasting serum total cholesterol, LDL-C , HDL-C and LDL-C / HDL-C at baseline and post-intervention in the 2 groups

		Control	n-3 fatty acid
Total cholesterol (mg/dL)	Baseline	246 (41.0)	239 (33.1)
	Post intervention	233 (32.1)	230 (42.1)
LDL-C (mg/dL)	Baseline	162 (34.1)	155 (40.4)
	Post intervention	164 (45.1)	152 (39)
HDL-C (mg/dL)	Baseline	37 (3.1)	37 (8.2)
	Post intervention	36 (8.9)	36 (9.1)
LDL-C/LDL-C	Baseline	4.3 (1.5)	4.1 (0.8)
	Post intervention	4.6 (2.1)	4.2 (1.7)

Numbers represent mean (SD).

Table 4. Fasting serum triglycerides, TG/HDL-C and MDA at baseline and postintervention in the 2 groups

		Control	n-3 fatty acid
TG (mg/dL)	Baseline	299 (37)	298 (48)
	Post intervention	308 (38)	220 (38)
TG/HDL-C	Baseline	8 (3.2)	8 (2.1)‡
	Post intervention	8.5 (3.7)	6.1 (2.5)
MDA (nmol/mL)	Baseline	2.7 (1.3)	2.5 (0.8)
	Post intervention	2.8 (1.4)	3.1 (1.0)

Numbers represent mean (SD).
* P < 0.003 Compared to post intervention; † P < 0.01 Compared to control group; ‡ P < 0.05 Compared to post intervention; § P < 0.05 Compared to control group

LDL-C); it is beneficial only in healthy reproductive age or postmenopausal women receiving HRT.[10]

Kurabayashi et al reported that estrogen or ombined HRT causes a decrease in serum TC and LDL-C and an increase in HDL-C resulting from increased hepatic LDL-receptor activity and suppressed hepatic TG lipase activity; it also causes an increase in TG resulting from suppression of lipoprotein lipase. Hence combination therapy with n-3 fatty acids and HRT might prevent hypertriglyceridemia caused by HRT,[3] which was consistent with our findings. The above-mentioned studies were not placebo controlled and daily dietary intake was not considered, making the results difficult to interpret.

Stark et al showed that n-3 fatty acid supplementation in postmenopausal women receiving or not receiving HRT decreased serum TG by 26 % on the whole.[4]

TG/HDL-C was significantly decreased at the end of study compared to initial values ($p<0.05$) and also at the end of the study compared to the control group ($p<0.05$). TG/HDL-C has been shown to be strongly associated with the risk of myocardial infarction[4] and to be a possible marker for the progression of atherosclerosis.[5] The significant decrease of TG/HDL-C after n-3 fatty acid

supplementation in this study is associated with decrease in risk of CVD and the prevention of the transition from atherosclerosis to atherothrombosis.[5] Both TG and HDL-C are major determinants of LDL partical size, partly due to the exchange of TG from VLDL for cholesterol ester in LDL, which is mediated by cholesterol ester transfer protein (CETP). It is possible that as serum TG decreases after n-3 fatty acids supplementation, less TG is transferred to LDL by CETP, reducing the formation of TG-enriched LDL, which minimizes the opportunity for lipoprotein lipase to convert large LDL particles to small LDL particles.[13] Consequently, the large amount of LDL consists of buoyant LDL, which has a limited ability to penetrate to the intima, and its oxidation effects are fewer than with small, dense LDL particles.[2,13] The effects of increased consumption of the n-3 fatty acids, on MDA (lipid peroxidation) have been contradictory.[23] In the present study, in the n-3 fatty acid group, there was no significant change in MDA during the study, contradictory to the results shown by Jenkinson,[24] Foulon,[25] Harats[26] and similar to the results shown by Stalenhoof,[15] Wander[23] and Higdon.[27]

The contradictory nature of these studies may be related to the assays of serum MDA, duration of supplementation, lipoprotein phenotype of the women and the purity and dosage of n-3 fatty acids. In the present study n-3 fatty acids had no significant effect on TC, which was confirmed by Mori[13] and Schectaman.[17] Torres et al reported that when n-3 fatty acids are consumed along with a diet low in saturated fat, there may be concomitant decrease in TC;[14] however, in the present study, there was no significant change in saturated fat intake in postmenopausal women and diets were not low in saturated fat (more than 11% of total calories). Decrease in serum TC and LDL-C due to n-3 fatty acids intake in postmenopausal women has been reported by Lox[10] and Kurabayashi[3] but daily dietary intake was not considered. In the present study, there was no significant change in LDL-C in the n-3 fatty acids group but an increase in LDL-C has been reported by most of the previous studies.[4,13,18,28] The increase in LDL may be explained, in part, by a down-regulation of the LDL-receptor, variations in the amount of n-3 fatty acids consumed and the manner in which they are presented (in fish, fish oil or nonpurified oil containing cholesterol and saturated fat). But in the present study, women consumed purified n-3 fatty acids without cholesterol and saturated fats; moreover the n-3 fatty acids were in TG form, having a greater absorption compared to the methyl ester form.[29] There is evidence that LDL particle size increases with n-3 fatty acids supplementation; it was suggested that this may reduce the atherogenic potential of LDL,[13] although further study is needed to confirm this. LDL-C/ HDL-C considered to be predictors of CHD risk[30] did not change significantly in this study. This further emphasizes the importance of routinely monitoring the effects of intervention strategies on TG/HDL-C.

In conclusion, this study showed that purified n-3 fatty acids reduced serum TG significantly, by 26%, in postmenopausal women. This effect was estimated to decrease the risk of CHD by 32% in postmenopausal women. In addition, n-3 fatty acids supplementation was effective in reducing TG/HDL-C by 23%. Further studies are needed to elucidate the interactions of n-3 fatty acids supplementation with specific HRT regimens and to determine the long-term effects of n-3 fatty acid supplementation on CVD events and mortality in postmenopausal women.

Acknowledgments

We thank Mrs. Chamari for technical assistance, Dr. Shahin Yarahmadi for screening of postmenopausal women, and Dr. Eshraghian for statistical counseling.

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