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Original Scientific Paper

EFFICACY OF A LIPID-LOWERING DIET ON KEY FATTY ACID RATIOS AND OMEGA-3 INDEX IN HYPERLIPIDEMIC SUBJECTS

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SUMMARY – Polyunsaturated fatty acid (PUFA) dietary intake, status and serum key fatty acid (FA) ratios may aid in cardiovascular disease-related risk assessment. The aim of this study was to investigate the effects of lipid-lowering diet on key FA ratios in serum phospholipids and omega-3 index in erythrocyte phospholipids in moderately hyperlipidemic subjects. The study included 41 subjects, mean age 56±6 years. Nutritional habits were evaluated by food frequency questionnaire. Participants followed lipid lowering diet for 12 weeks. Energy intake of omega-6 and omega-3 FA was changed from 7.6% and 0.6% to 5.7% and 1.2%, respectively. Marked decrease in four FA ratios in serum phospholipids, i.e., omega-6/omega-3, arachidonic acid (AA)/eicosapentaenoic acid (EPA), AA/docosahexaenoic acid (DHA), AA/(EPA+DHA) and omega-3 index (EPA+DHA) was found in study subjects after lipid-lowering diet. Total cholesterol/high-density lipoprotein (HDL), low-density lipoprotein (LDL)/HDL and triacylglycerol/HDL-cholesterol ratios positively correlated with all FA ratios, and negatively correlated with total omega-3 levels in serum phospholipids and omega-3 index in erythrocytes. Total serum omega-3 levels showed strongest association with lipoprotein ratios and positive correlation with homeostatic model assessment (HOMA) index. In conclusion, lipid-lowering diet resulted in decreased serum key FA ratios, increased omega-3 levels, and improved insulin sensitivity that may lead to a lower risk of cardiovascular disease in subjects with moderate hyperlipidemia.

Key words: *Fatty acid ratio; Hyperlipidemia; Lipid-lowering diet; Omega 3-index; TG/HDL*

Introduction

Polyunsaturated fatty acids (PUFA) of omega-6 and omega-3 series are important factors in human nutrition. Imbalance of their intake, status and plasma key fatty acid (FA) ratios are linked with metabolic and cardiovascular diseases (CVD)[1-3]. Persons with cardiometabolic risk factors represent a group with high lifetime risk of CVD. They most frequently have dyslipidemia (low high-density lipoprotein (HDL)-cholesterol, increased triacylglycerol (TG), and/or an increased number of small low-density lipoprotein (LDL) particles). Additionally, disturbed blood lipids are related to atherosclerosis, and TG/HDL-cholesterol ratio classifies persons with dyslipidemia, insulin resistance and CVD[4,5]. High dietary omega-6/

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omega-3 PUFA ratio is mirrored to PUFA status in plasma, and is also associated with an increased risk of obesity and CVD[2,6]. As a consequence of general recommendations to replace saturated with unsaturated fats, dietary intake of omega-6 markedly increased at the expense of omega-3 PUFA worldwide over the past decades. Although the recommended dietary ratio between omega-6 and omega-3 is 4-5, it often exceeds 20 in Western diet[6]. Still, studies on healthy people have uniformly reported that replacing saturated fats with PUFA (largely of omega-6 series) reduced total cholesterol (TC) and LDL-cholesterol and led to a decreased TC/HDL-cholesterol ratio[4,7].

Previous studies revealed that dietary intake of essential omega-6 and omega-3 PUFA highly correlated with their level in serum and erythrocyte phospholipids[1,8]. FA analyses of serum/plasma phospholipids, a recognized biomarker of eicosapentaenoic acid (EPA, 20:5 ω-3) and docosahexaenoic acid (DHA 22:6 ω-3) intakes, showed an inverse correlation between omega-3 PUFA and particularly DHA levels and the development of coronary heart disease (CHD)[2,9,10]. Furthermore, population studies demonstrated the percentages of total omega-3 ≥7.2% to be associated with a 31% lower risk of CHD[9,10]. The proportion of DHA ≥4.5% of total plasma/serum phospholipid FA reduced the risk of CHD by 34%[10].

Serum cholesterol is also a well-established primary risk factor for CHD. Lipid lowering diets remain the first-line treatment for reducing serum lipids in patients with hyperlipidemia in an attempt to decrease the risk of CHD. The US National Cholesterol Education Program (NCEP) Step 1 diet implies the total dietary fat intake of maximal 30% or less of total calories, saturated fat intake of less than 10%, and up to 300 mg daily of dietary cholesterol intake[11]. We have previously found that subjects with hyperlipidemia on Step 1 diet had better serum lipid profile with decreased TC/HDL and LDL/HDL ratios, as well as serum and erythrocyte FA profiles[12]. In order to optimize the prognostic value of the lipid panel, now we calculated the TG/HDL ratio. According to a recent research, the TG/HDL cut-off points that predict insulin resistance and increased cardio-metabolic risk were 2.5 for women and 3.5 for men[4]. Research into the potential benefits of omega-3 FA will continue and should include FA blood measurements in individual patients[13]. In view of the FA ratios as the potential new cardiovascular risk factor, we retrospectively analyzed our previous data. Therefore, primary aim of this study was to examine the effects of a lipid-lowering diet on key FA ratios in serum phospholipids and omega-3 index in erythrocyte phospholipids in subjects with moderate hyperlipidemia. Secondary, we evaluated whether there was a correlation between FA ratio and lipoprotein ratio.

Subjects and Methods

The criteria for inclusion in the study were based on the previously reported NCEP Step 1 diet strategy for CHD prevention[12]. In brief, moderate hyperlipidemic subjects (no evidence for CVD disease), median age 56 (45-65) years, body mass index (BMI) <30 kg/m^2 were recruited to the study. Moderate hyperlipidemia was defined as an LDL-cholesterol level of 3.39-4.91 mmol/L and no use of any hypolipidemic drugs for at least 12 weeks prior to the study. Subjects who had evidence for any chronic disease, including liver or kidney dysfunction, cardiovascular or thyroid dysfunction, and diabetes mellitus, and those who were taking hormone-replacement therapy, antioxidant supplements or any other medications were excluded. Individuals who smoked and those with an alcohol intake of more than 30 g *per* day and/or were taking fish, flaxseed, or walnuts in more than 2 servings/week were also excluded.

Out of a cohort of 157 free-living potential respondents selected for enrolment in the study at the Centre of Research Excellence in Nutrition and Metabolism, Institute for Medical Research in Belgrade, 41 subjects (13 men and 28 postmenopausal women aged 56±6 years) accepted to be involved in medical nutrition therapy for lowering serum lipoproteins. In addition, 20 sex- and age-matched healthy, normolipidemic and normal-weight volunteers, were included as controls. The study protocol was approved by the University ethics review boards and performed in accordance with the Declaration of Helsinki. All study participants signed an informed consent form prior to their involvement in the study.

The participants followed Step 1 lipid lowering diet for 12 weeks. The Step 1 diet is a strategy for the prevention of CHD in individuals with LDL-cholesterol concentrations ≥4.1 mmol/L or in those with a borderline high LDL-cholesterol concentration (3.36-4.11 mmol/L) and ≥2 cardiovascular risk factors (cigarette smoking, hypertension, low HDL cholesterol, family history of premature CHD, and age [men 45 years and women ≥55 years]). Habitual

dietary intake of study participants before and after the diet period was assessed using a validated semi-quantified food frequency questionnaire (FFQ), which contained 142 food items and beverages commonly consumed in Serbia[12,14]. Dietary intake for our participants was prescribed individually to maintain the habitual daily caloric intake throughout the study period with changes in nutrient proportions according to Step 1 diet recommendation[11]. Dietary treatment target and assessment of dietary intake we described in our previous paper[12], and now we only note that restricted food included high-fat meat and dairy products, frying with sunflower oil (the most popular cooking method in Serbian population), ≥2 eggs/week, fried food, cream sauces, high-fat pastries and sweets. In addition, the participants kept daily food diaries during the 12-week period of dietary habit modification while maintaining their habitual level of physical activity and learned about proper daily nutrition through weekly lectures and counseling by skilled dietitians. Two participants left the study, for reasons unrelated to the study.

Blood samples from all study participants were collected at the start and at the end of the intervention period, in the morning, 12 h after the last meal and 48 h without alcohol consumption. Plasma lipids were determined as described previously[12]. Plasma glucose was measured by using standard enzyme color tests (EliTech Diagnostic, Sées, France). Insulin level was determined by the radioimmunoassay (INEP Zemun, Belgrade, Serbia). Fasting insulin and glucose concentrations were used to calculate insulin resistance from the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR model: insulin × glucose/22.5). As previously reported, serum and erythrocyte lipids were extracted according to the method of Sperry, Brand and Harth, respectively[12].

The procedure for FA analysis has been described previously[12]. Methyl ester derivatives were analyzed on a Shimadzu 2014 gas chromatograph fitted with a capillary column (Rtx 2330, Restek, USA). Individual FA methyl esters were expressed as relative percentage of total identified FA (mol %). The omega-3 index was expressed as the sum of EPA and DHA in erythrocyte phospholipids.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Calculations were made for total omega-6/total omega-3, AA/EPA, AA/DHA, AA/(EPA+DHA). All variables demonstrated normal distribution, as shown by Kolmogorov-Smirnov test. Differences between baseline and post-treatment period were analyzed using paired Student's t-test. Pearson post-intervention correlation coefficients were computed to examine the associations of lipoprotein ratios and FA ratio, total omega-3 FA in serum phospholipids, and omega-3 index in erythrocyte phospholipids at the end of the study. The SPSS 20 software (IBM, Armonk, NY, USA) was used on statistical analysis and p values <0.05 indicated statistical significance.

Results

Forty-one subjects (13 men and 28 postmenopausal women) began the study and 39 completed it. Participants maintained their initial dietary energy intake throughout the study period. Body weight did not change during the diet period. The percentage of energy from protein intake did not change for subjects on lipid-lowering diet but carbohydrate intake increased approximately by 7% (from 48% to 55% due to greater consumption of grain/high-fiber food and fruit) from habitual diet. During the treatment period, dietary saturated and polyunsaturated fat intake decreased by 7% and 1.5%, respectively, and intake of monounsaturated fat increased by 1.5% (data not shown). Dietary intervention changed the intake of total omega-6 and total omega-3 FA *per* day from 7.6% to 5.7% and from 0.6% to 1.2%, respectively (Table 1). Thus, dietary total omega-6/omega-3 ratio decreased from 12.8 to 4.8.

Table 1. Omega-6 and omega-3 dietary fatty acid intake in study participants

	Baseline	End point
ω-6 (%)	7.62±0.96	5.72±0.59***
LA (g/day)	19.03±2.27	14.19±1.46***
AA (g/day)	0.16±0.03	0.12±0.02***
ALA (g/day)	1.38±0.28	2.37±0.13***
EPA+DHA (g/day)	0.17±0.02	0.64±0.05***
ω-3 (%)	0.61±0.161	1.20±1.10***
ω-6/ω-3	12.83±2.88	4.78±0.61***

Values are means ± standard deviation ***p≤0.001 significantly different from baseline; LA = linolenic acid; AA = arachidonic acid; ALA = alfa-linolenic acid; EPA+DHA = eicosapentaenoic + docosahexaenoic acid; PUFA = polyunsaturated acid

As presented in Table 2, lipid-lowering diet significantly decreased TG/HDL-cholesterol ratio after 12 weeks (p<0.001). Also, a significant decrease in fasting glucose (p<0.001), fasting insulin (p<0.01) and calculated HOMA-IR (p<0.001) was observed in moderately hyperlipidemic subjects.

Table 2. TG/HDL ratio and glucose tolerance parameters in study subjects

Serum	Baseline	End point
TG/HDL-cholesterol	1.69±0.41	1.13±0.39***
Fasting glucose (mmol/L)	4.91±0.43	4.52±0.46***
Fasting insulin (mU/L)	16.57±3.18	14.44±3.03**
HOMA-IR	3.62±0.88	2.90±0.67***

Values are means ± standard deviation; **p≤0.01, ***p≤0.001 significantly different from baseline; HDL-C = high-density lipoprotein cholesterol ratio; TG = triacylglycerol; HOMA-IR = homeostasis model assessment method for insulin resistance

At baseline, when comparing moderately hyperlipidemic subjects to healthy controls, three important FA ratios in serum phospholipids, i.e., omega-6/omega-3, AA/DHA and AA/(EPA+DHA) were significantly higher (Table 3). Serum total omega-3 FA and erythrocyte omega-3 index were significantly lower in moderate hyperlipidemia.

Markedly decreased (p<0.001) key FA ratios in serum phospholipids, omega-6/omega-3, AA/EPA, AA/DHA and AA/(EPA+DHA) were found in participants after therapeutic diet (Table 3). Serum total omega-3 FA and erythrocyte omega-3 index were significantly higher after 12 weeks. When comparing moderately hyperlipidemic subjects after diet to healthy controls, omega-6/omega-3 and AA/EPA ratios were significantly lower while AA/DHA and AA/(EPA+DHA) ratios were similar to those in controls. However, increased omega-3 index after lipid-lowering diet was still significantly lower in study subjects than in controls.

Table 4 summarizes the results of correlation analyses, which indicated that TC/HDL, LDL/HDL and TG/HDL-cholesterol ratios negatively correlated with total omega-3 levels in serum phospholipids and omega-3 index in erythrocytes. Furthermore, these lipoprotein ratios positively correlated with AA/EPA,

Table 3. Serum phospholipid fatty acid ratio and omega 3-index recorded in study subjects

Serum phospholipid	Control group	Treatment baseline	Treatment end point
Total omega 3	4.95±0.97	4.05±0.31[c]	4.84±0.34***
Total omega 6/omega 3	9.06±1.66	9.43±0.95	8.43±0.66[a]***
AA/EPA	37.25±10.98	40.29±8.11	31.82±5.95[c]***
AA/DHA	3.26±0.81	3.7±0.50[b]	3.22±0.40***
EPA+DHA	4.25±0.89	3.34±0.32[c]	4.11±0.33***
AA/EPA+DHA	2.98±0.73	3.38±0.42[b]	2.91±0.34***
Erythrocyte phospholipids: omega-3 index (% EPA+DHA)	6.24±0.94	4.19±0.41[c]	4.50±0.46[c]***

Values are means ± SD; [a]p≤0.05, [b]p≤0.01 and [c]p≤0.001 significantly different from control group, ***p≤0.001 significantly different from baseline; AA = arachidonic acid; EPA+DHA = eicosapentaenoic + docosahexaenoic acid

Table 4. Correlation matrix of lipoprotein ratio and HOMA-IR with key fatty acid ratios

	TC/HDL-C	LDL/HDL-C	TG/HDL-C	HOMA-IR
AA/EPA	r=0.380**	r=0.348*	r=0.304**	r=0.146
AA/DHA	r=0.279*	r=0.223*	r=0.320**	r=0.220
AA/EPA+DHA	r=0.315**	r=0.256*	r=0.349**	r=0.234
Total serum omega 3	r=-0.493**	r=-0.404**	r=-0.563**	r=-0.291*
Total omega 6/omega 3	r=0.364**	r=0.291**	r=0.416**	r=0.176
Omega-3 index (% EPA+DHA)	r=-0.271*	r=-0.235*	r=-0.351**	r=-0.105

*p<0.05, **p<0.01, AA = arachidonic acid; EPA+DHA = eicosapentaenoic + docosahexaenoic acid

AA/DHA, AA/(EPA+DHA) and total omega-6/omega-3 ratios. The proportion of omega-3 PUFA in serum phospholipids had the strongest negative association with TG/HDL ratio (r=-0.563, p=0.001). Among key FA ratios, only omega-3 PUFA in serum phospholipids significantly correlated with HOMA-IR (r=-0.291, p=0.033).

Discussion

Our study showed that changes in dietary habits according to a lipid-lowering diet (although baseline energy intake *per* day remained unaltered) resulted in markedly decreased serum key FA ratios (total omega-6/omega-3, AA/EPA, AA/DHA and AA/(EPA+DHA), TG/HDL ratio), as well as increased serum omega-3 FA and erythrocyte omega-3 index, which all may lead to a lower cardio-metabolic risk in subjects with moderate hyperlipidemia. After dietary treatment, serum omega-6/omega-3 and AA/EPA ratio were significantly lower in the study participants compared to control subjects. At the same time, we found that after 12 weeks, the lipid-lowering diet induced favorable changes in insulin resistance parameters too.

The estimation of dietary fat intake is a valuable first step in clinical decision making about dietary and pharmaceutical advice in order to decrease the risk of CVD[15]. At the beginning of the study, participants started to follow lipid-lowering diet treatment belonged to the high-risk category for CVD according to the baseline FA ratios[16]. Markedly decreased serum key FA ratios formed a potentially less atherogenic FA profiles in our study participants after the lipid-lowering diet. Decreased dietary intake of total, saturated and omega-6 fats and increased omega-3 fat consumption reduced dietary total omega-6/omega-3 ratio from the very high baseline 12.8 to favorable 4.8 ratio. An approximate dietary intake of 6% omega-6 and 1% omega-3 FA has been recommended to achieve desirable effects on these essential FAs[2,3]. Generally, as previously reported, during treatment period, participants had the same dietary protein intake, lower total fat intake (35% *vs*. 29%), and higher carbohydrate intake (48% *vs*. 55%), due to greater consumption of grain/high-fiber food and fruit, although total energy intake remained unaltered[12].

Nevertheless, after dietary treatment, study participants still had an increased risk of CVD, based on the reported cut-off values for omega-3 FA in relation to the proposed therapeutic goals[13,16]. The cut-off value for the sum of EPA+DHA in serum/plasma phospholipids was ≥4.6% for a lower risk category of fatal ischemic heart disease[10]. Lipid-lowering diet increased EPA+DHA serum phospholipid levels from 3.3% to 4.1% in our study participants, while total omega-3 levels raised from 4.0% to 4.8%. The amount of EPA and DHA in the diet and their content in serum and cell phospholipids could improve plaque stability, decrease systemic inflammation and development of atherosclerosis *via* diverse mechanisms[17,18]. Besides, omega-3 index in the erythrocytes is also a potential risk factor for CHD mortality; an index of ≥8% was related to the highest cardioprotection, while an index of <4% was least cardioprotective[19]. Omega-3 index in the participants with hyperlipidemia slightly increased from 4.2% to 4.5%, but it was still significantly lower as compared with those without hyperlipidemia.

Increased synthesis of long-chain PUFA is important for membrane functions in most tissues, including endothelium and platelets. Accordingly, the AA to EPA ratio can be used as a diagnostic parameter for assessing the impact of pro-inflammatory eicosanoids and cytokines[20]. Recently, Ito *et al*.[21] found that obese dyslipidemic subjects had lower EPA/AA ratio than non-obese persons with dyslipidemia. The same authors have reported that low EPA/AA ratio is associated with the incidence of cardiac death and myocardial infarction[19]. We found a statistically significant increase in omega-3 FA with decreased AA/EPA ratio at the end point of dietary treatments. We consider this finding of special importance considering the negative association of omega-3 FA in serum and erythrocytes with CVD and metabolic syndrome[22,23]. Low omega-3 FA content in erythrocyte membrane, commonly present in dyslipidemic and hypertensive patients[22,23], leads to low-grade inflammation due to intensified metabolism of pro-inflammatory mediators[24,25].

It has been well documented that long-term omega-3 FA supplementation decreases fasting triglyceride concentrations[26,27]. Analysis of 36 human crossover studies found that 3-4 g/d EPA+DHA intake yielded a plasma triglyceride decrease of 24% and 35% in normolipidemic and hypertriglyceridemic subjects, respectively[27]. There is a body of evidence that the TG/HDL-cholesterol ratio is related to cardio-metabolic diseases, but also predicts the risk of developing cardiovascular accidents in the general population[4,5]. Thus, the TG/HDL-cholesterol ratio showed negative correlation with total omega-3 FA in serum phospholipids and erythrocyte omega-3 index in our

participants with hyperlipidemia. Alterations in blood lipids can have an impact on the composition, content and distribution of different plasma lipoproteins that can change the risk of atherosclerosis[28]. It has also been reported that decreasing dietary omega-6/omega-3 FA to approximately 3:1 in older individuals by increasing the intake of EPA and DHA lowered fasting and postprandial plasma triglyceride concentrations, but also decreased the proportion of small dense LDL, while the proportion of HDL2 increased[22,29]. Although our study participants did not achieve this dietary ratio of omega-6/omega-3 FA, it was markedly decreased in serum phospholipids after the diet.

Our study also revealed significant correlations between key FA indexes and serum lipoproteins. Namely, people with hyperlipidemia, especially those with coexisting elevated triacylglycerol levels, should be screened for serum and erythrocyte omega-3 FA biomarkers. A recently published paper suggests that TG/HDL-cholesterol is the most clinically useful tool for discrimination of insulin resistance in persons with normal weight[5]. Furthermore, higher AA/EPA ratio is associated with insulin resistance in young adults[30] and visceral fat accumulation in male subjects[31]. A positive correlation between omega-6/omega-3 ratio and HOMA-IR index has also been reported in persons with metabolic syndrome[32]. Here we found a negative correlation of HOMA-IR with the levels of omega-3 FA and positive association with AA/DHA ratio in serum phospholipids in participants with hyperlipidemia, but correlation for AA/EPA ratio was not statistically significant. Future studies examining the association of waist circumference and serum key FA may be important in the cardiovascular risk assessment[33].

This study had several limitations. The first was the relatively small number of study participants that could limit statistical power of our results. Secondly, we did not divide study participants according to gender. Women usually show a more favorable metabolic risk profile than men, including lower triglyceride and higher HDL-cholesterol levels[34]. Dietary FA intake was assessed by validated FFQ and compliance was measured as a change in the serum phospholipid FA composition. Yet, despite these limitations, the status biomarker of dietary FA intake showed good subject compliance, which means that the participants were adherent to the dietary intervention.

In conclusion, changes in dietary habits according to cholesterol lowering diet resulted in improved serum key FA ratios and omega-3 index, which may lead to a lower CVD risk. Changes in FA profiles were found after 12 weeks of dietary intervention, and longer diet would probably lead to an even greater improvement. Future studies are warranted to assess whether dietary balance of omega-6/omega-3 PUFA or absolute intake of EPA and DHA are more important in the prevention and treatment of dyslipidemia and glucose homeostasis in moderately hyperlipidemic subjects.

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Sažetak

UČINKOVITOST DIJETE ZA SNIŽAVANJE LIPIDA NA KLJUČNE OMJERE MASNIH KISELINA I OMEGA-3 INDEKS KOD OSOBA S HIPERLIPIDEMIJAMA

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Prehrambeni unos polinezasićenih masnih kiselina (MK), status i ključni omjeri MK u serumu mogu biti od pomoći u procjeni rizika za kardiovaskularne bolesti. Cilj ove studije bio je istražiti učinke prehrane koja snižava lipide na ključne omjere MK u fosfolipidima (FL) seruma i omega-3 indeks u FL eritrocita kod osoba s umjerenom hiperlipidemijom. U istraživanju je sudjelovala 41 osoba prosječne dobi 56±6 godina. Prehrambene navike ocjenjivane su upitnikom o učestalosti konzumiranja hrane. Sudionici su 12 tjedana bili na dijeti. Unos energije iz omega-6 i omega-3 MK promijenjen je sa 7,6% i 0,6% na 5,7% i 1,2%. Nakon dijete smanjeni su omjeri MK u FL seruma: omega-6/omega-3, arahidonska kiselina (AA)/eikosapentaenska kiselina (EPA), AA/dokozaheksaenoinska kiselina (DHA), AA/(EPA+DHA) i omega-3 indeks (EPA+DHA). Omjer ukupnog kolesterola/HDL-a, LDL/HDL-a i triacilglicerola/HDL-kolesterola pozitivno je korelirao sa svim omjerima MK, a negativno s ukupnim razinama omega-3 u FL seruma i omega-3 indeksom u eritrocitima. Ukupne omega-3 u serumu pokazale su značajnu povezanost s omjerima lipoproteina i pozitivnu koleraciju s indeksom HOMA. U zaključku, dijeta sa smanjenim unosom lipida dovela je do smanjenja ključnih omjera MK u serumu, povišenja razine omega-3 i poboljšanja osjetljivosti na inzulin, što može dovesti do nižeg rizika za kardiovaskularne bolesti kod osoba s umjerenom hiperlipidemijom.

Ključne riječi: *Omjer masnih kiselina; Hiperlipidemija; Dijeta za snižavanje lipida; Omega-3 indeks; TG/HDL*