Original Article

Plasma ω-3 fatty acid levels negatively and ω-6 fatty acid levels positively associated with other cardiovascular risk factors including homocysteine in severe obese subjects

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Obesity and homocysteine (tHcy) are important risk factors for cardiovascular diseases (CVD). Plasma omega-3 fatty acids (ω-3 FAs) and omega-6 fatty acids (ω-6 FAs) are essential fatty acids with diverse biological effects in human health and disease. We have investigated the relation of plasma ω-3 FAs and ω-6 FAs levels with other cardiovascular risk factors including tHcy in severe obese subjects. This study was performed on 96 severe obese and 65 normal weight subjects. Plasma fatty acid composition was measured by GC/MS and serum tHcy level was measured by HPLC methods. There were no differences between groups in terms of concentrations of serum tHcy, plasma ω-3 FAs, ω-6 FAs and ω-3/ω-6 ratio, whereas serum vitamin B-12 ($p<0.01$) and folic acid ($p<0.05$) levels were lower than those of the normal weight subjects. Homocysteine positively correlated with ω-6 FAs and negatively correlated with ω-3 FAs in severe obese and normal weight subjects. Serum vitamin B-12 positively correlated with ω-3 FAs ($p<0.01$) and ω-3/ω-6 ratio ($p<0.01$) and negatively correlated with ω-6 FAs ($p<0.05$) in severe obese subjects. Serum folic acid positively correlated with ω-3 FAs ($p<0.01$) in severe obese subjects. Our results suggest an association between the plasma ω-3 FAs and ω-6 FAs and serum tHcy concentrations in severe obese and normal weight subjects. Low levels vitamin B-12 and folic acid may have been responsible for the elevated tHcy levels in severe obese subjects, increasing the risk for future development of cardiovascular diseases.

Key Words: ω-3 fatty acids, ω-6 fatty acids, homocysteine, obesity, vitamin B-12

INTRODUCTION

Obesity induces marked metabolic disturbances that contribute to the pathogenesis of cardiovascular diseases (CVD), and it is associated with a marked increase in morbidity and mortality.[1,2] Homocysteine (tHcy) is derived from the metabolic conversion of the essential amino acid methionine. Homocysteine is believed to cause atherogenesis and thrombogenesis via endothelial damage, vascular smooth muscle proliferation and coagulation abnormalities.[3,4] In the remethylation pathway of tHcy to methionine, vitamin B-12 and folic acid act as cofactors.[5] The triad tHcy-vitaminB-12-folic acid has received much attention in atherosclerosis research in recent years and elevated serum total tHcy may be a marker of the progression of the atherosclerotic process.[6,7] In the general population, supplementation with folic acid and vitamin B-12 can reduce tHcy concentrations by approximately 33%.[6]

Omega-3 fatty acids (ω-3 FAs) are defined as linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic (DHA),[8] and omega-6 fatty acids (ω-6 FAs) are defined as linoleic and arachidonic acid.[9] Omega-3 FAs are the most important fatty acids with a preventive function for cardiovascular disease via reduction of blood pressure,[10] and serum triacylglycerol levels,[11] antithrombotic effect, anti-inflammatory effect, and increase in heart rate variability.[12] Excessive amounts of ω-6 FAs and a very high ω-6/ω-3 ratio, as is found in today's western diets, promote the pathogenesis of many diseases, including CVD, cancer, and inflammatory and autoimmune diseases.[13] The association between serum tHcy and dietary fish and ω-3 FAs has been studied; with inconsistent findings.[14-16] It has been hypothesized that a high intake of ω-3 FAs may reduce tHcy but only in combination with a high B vitamin intake.[17] Furthermore, study authors have suggested that the mechanisms for reduced tHcy concentrations may be attributed to possible fish oil induced oxidative stress and stimulation of the oxidative catabolism of tHcy, the alteration of cysteine / tHcy ratios via the trans sulphuration pathway, and the inhibition of methionine synthase activity with fish oil supplementation by way of enhanced nitrous oxide production.

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Manuscript received 21 October 2011. Initial review completed 30 March 2012. Revision accepted 7 May 2012.

Many factors have been found to be associated with plasma tHcy concentration.[18] However, only few studies have addressed the relation between serum tHcy and plasma ω-3 FAs and ω-6 FAs levels.[16,17] Furthermore, no study has been published on the correlation between serum tHcy, vitamin B-12, folic acid levels and plasma ω-3 FAs and ω-6 FAs levels in severe obese subjects. Therefore, we performed this study to examine the association of plasma ω-3 FAs and ω-6 FAs levels with other CAD risk factors including serum tHcy concentrations in severe obese and normal weight subjects.

MATERIAL AND METHODS

Participants

This study was performed on 96 (25 men, 71 women) severe obese people aged 21-60 years (mean 40.6±10.1) and 65 (21 men, 44 women) healthy normal weight subjects aged 21-60 years (mean 38.3±9.2). The obese subjects and healthy controls were examined in Internal Clinics of Meram Medical School by a specialized internalist. Anthtropometric measures and laboratory findings of the subjects are given in Table 1. Body mass index (BMI) was used as obesity criteria. BMI of the obese subjects was more than 35 kg/m^2 and that of healthy controls was less than 25 kg/m^2. There were no complaints and symptoms of the obese subjects other than obesity. Exclusion criteria for the study included malignant disease, diabetes mellitus, chronic liver disease, chronic kidney disease infectious disease, hypertension, a history of CVD and taking a supplement fish oil tablets.

The study protocol was approved by the Ethics Committee of Meram Medical School, University of Selcuk, Konya, Turkey. All patients were informed of the details of the study and written consent of each patient was received.

Anthropometric measurements

All anthropometric measurements were taken with participants wearing light clothing and no shoes. BMI was measured in all participants. BMI was calculated as weight (in kg) divided by height (in m) squared, and participants waists were measured with a soft tape midway between the lowest rib and the iliac crest. The hip circumference was measured at the widest part of the gluteal region.

Biochemical analyses

Blood samples were obtained after overnight fasting in empty vacuum tubes and in tubes containing EDTA. Plasma and serum samples were obtained after suitable centrifugation and samples were stored frozen at -80 ^{o}C until the day of plasma FAs and serum tHcy analysis. Serum lipids, vitamin B-12 and folic acid levels were measured immediately.

Analysis of FAs

Plasma FAs concentrations were measured using a modification of the method described by Lagerstedt *et al*,[19] and using an internal standard mixture (Larodon-Lipids KT 90-1100). Analysis was performed on a Shimadzu Qp 2010 gas chromatography-electron-capture negative-ion mass spectrometry (GC/MS). The plasma FAs concentration values are reported in mg per liter (mg/L). Total ω-3 FAs is presented as the sum of EPA, DHA and linolenic acid, and total ω-6 fatty acids as the sum of arachidonic and linoleic acid.

Homocysteine measurements

Serum tHcy concentrations were measured using the Chromsystems (Munich, Germany) reagent kit for HPLC technique with fluorescence-detector. The serum tHcy concentration values are reported in μmol per liter (μmol/L). The referance range of serum tHcy concentrations are 5.5 to 14 μmol/L in our laboratory.

Measurement of other analytes

Serum total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-cholesterol), low density lipoprotein cholesterol (LDL-cholesterol) and glucose were measured by commertially available kits based on routine methods on the Synchron LX System (Beckman Coulter, Fullerton CA). Serum vitamin B_{12} and folic acid levels were determined by routine methods on E170 analyzer (Roche Diagnostics). The referance range of serum vitamin B-12 and folic acid concentrations are 191 to 663 pg/mL and 3.1 to 17.5 ng/mL in our laboratory.

Statistical analysis

All data are expressed as mean±standard deviations (SD). Statistical analyses were done using SPSS v16.0 (SPSS Inc, IL, USA). The normality of the variables was evaluated using the one-sample Kolmogorov-Smirnov test. The normal distribution of variables were examined with independent-samples t test, and non-normally distributed variables were examined by Mann-Whitney U test. To compare the ratio of categorical variables, we used the chi-squared test. The correlations between variables were performed by Pearson's correlation test. Multiple linear regression analysis was performed among those significant variables in Pearson's correlation analysis. Also, we performed a univariate analysis of variance to compare the differences in serum tHcy, plasma ω-3 FAs and ω-6 FAs levels and ω-3/ω-6 ratios of normal weight subjects and severe obese subjects, and used age, sex, vitamin B-12 and folic acid as covariates. Differences were considered significant at a probability level of $p<0.05$.

RESULTS

Clinical characteristics and biochemical parameters of the subjects are presented in Table 1. As seen from the table, weight, BMI, waist circumference (WC), waist-to-hip ratio (WHR), total cholesterol, triglycerides, fasting blood glucose and LDL-cholesterol levels of the severe obese subjects were significantly higher ($p<0.01$ for total-cholesterol and LDL-cholesterol and $p<0.001$ for the other parameters) whereas HDL-cholesterol ($p<0.001$), serum B-12 ($p<0.01$) and folic acid ($p<0.05$) levels were lower than those of the normal weight subjects. After adjusting for age, sex, vitamin B-12 and folic acid there were no significant differences between serum tHcy, plasma ω-3 FAs, ω-6 FAs and ω-3/ω-6 ratios of the groups.

Simple correlation analysis was performed to investigate the association of serum tHcy, vitamin B-12 and

Table 1. Clinical characteristics and laboratory findings of severe obese and normal weight subjects[†]

	Control	Obese	*p*-value
n (M/F)	65 (21 M, 44 F)	96 (25 M, 71 F)	0.246
Age (years)	38.3 ± 9.2	40.6 ± 10.1	0.188
Weight (kg)	60.1 ± 9.2	115.6 ± 16.8	<0.001
BMI (kg/m^2)	23.0 ± 2.3	44.1 ± 5.9	<0.001
Waist circumference (cm)	76.7 ± 9.1	120 ± 10.9	<0.001
Waist-to-hip ratio	0.78 ± 0.06	0.88 ± 0.8	<0.001
Total cholesterol (mg/dL)	183 ± 37.3	199 ± 40.9	0.009
Triglycerides (mg/dL)	79.3 ± 39.9	164 ± 97.9	<0.001
HDL cholesterol (mg/dL)	50.9 ± 13.9	41.9 ± 11.5	<0.001
LDL cholesterol (mg/dL)	116 ± 34.3	124 ± 36.7	0.041
Fasting blood glucose (mg/dL)	85.1 ± 7.9	99.5 ± 11.2	<0.001
Serum homocysteine (μmol/L)	10.4 ± 3.5	13.4 ± 12.8	0.061
Serum vitamin B-12 (pg/mL)	313 ± 112	256 ± 107	0.001
Serum folic acid (ng/mL)	8.1 ± 2.6	7.3 ± 2.1	0.031
Total ω-3 Fatty acids(mg/L)	1.44 ± 1.7	1.67 ± 2.2	0.193
Total ω-6 Fatty acids (mg/L)	26.4 ± 8.4	26.2 ± 8.9	0.829
ω-3/ω-6 ratio	0.066 ± 0.1	0.072 ± 0.1	0.362

[†]All values (except gender) are mean±standard deviations. BMI, body mass index; HDL-cholesterol, high density lipoprotein-cholesterol; LDL-cholesterol, low density lipoprotein- cholesterol.

Table 2. Correlations of serum homocysteine, vitamin B-12 and folic acid with plasma ω-3 FAs, ω-6 FAs and the ω-3/ ω-6 ratio of severe obese and normal weight subjects

	Control (n=65)			Obese (n=96)		
	ω-3 FAs	ω-6 FAs	ω-3/ω-6 ratio	ω-3 FAs	ω-6 FAs	ω-3/ω-6 ratio
Homocysteine	-0.268*	0.298*	0.032	-0.207*	0.348**	-0.213
Vitamin B-12	0.027	-0.137	0.009	0.411**	-0.206*	0.427**
Folic acid	0.154	-0.209	0.055	0.292**	-0.145	0.010

ω-3 FAs, omega-3 fatty acids; ω-6 FAs, omega-6 fatty acids; * $p< 0.05$; ** $p< 0.01$

folic acid with plasma ω-3 FAs, ω-6 FAs and ω-3/ω-6 ratio, As shown in Table 2, the tHcy positively correlated with ω-6 FAs (r = 0.348, $p<0.01$) and negatively correlated with ω-3 FAs (r = -0.207, $p<0.05$) in severe obese subjects. Serum vitamin B-12 positively correlated with ω-3 FAs (r = 0.411, $p<0.01$) and ω-3/ω-6 ratio (r = 0.427, $p<0.01$) and negatively correlated with ω-6 FAs (r = -0.206, $p<0.05$) in severe obese subjects. Serum folic acid positively correlated with ω-3 FAs (r = 0.292, $p<0.01$) in severe obese subjects. Homocysteine positively correlated with ω-6 FAs (r = 0.298, $p<0.05$) and negatively correlated with ω-3 FAs (r = -0.268, $p<0.05$) in normal weight subjects.

Omega-6 FAs was positively correlated with cholesterol (r = 0.319, $p<0.01$) and LDL-cholesterol (r = 0.264, $p<0.05$) in severe obese subjects. On the other hand, ω-6 FAs positively correlated with cholesterol (r = 0.229, $p<0.05$) in normal weight subjects (Table 3). In addition, as shown in Table 4, tHcy negatively correlated with vitamin B-12 (r = -0.244, $p<0.05$) and folic acid (r = -0.332, $p<0.01$) in severe obese subjects and vitamin B-12 (r = -0.239, $p<0.05$) and folic acid (r = -0.268, $p<0.05$) in normal weight subjects.

On the other hand, tHcy positively correlated with BMI (r = 0.461, $p<0.01$), WC (r = 0.303, $p<0.01$), WHR (r = 0.332, $p<0.01$), weight (r = 0.493, $p<0.01$) in normal weight subjects, and serum vitamin B-12 (r = -0.219, $p<0.05$) negatively correlated with weight in severe obese subjects. In addition, tHcy positively correlated with cholesterol (r = 0.303, $p<0.01$), LDL-cholesterol (r = 0.361, $p<0.01$) and folic acid (r = 0.273, $p<0.01$) in severe obese subjects. Homocysteine negatively correlated with HDL-cholesterol (r = -0.269, $p<0.05$) in normal weight subjects (data not shown).

Multiple linear regression analysis was performed to determine the independent association of tHcy, vitamin B-12 and folic acid when controlled for FAs, such as ω-3 FAs, ω-6 FAs and ω-3/ω-6 ratio. The results shown that tHcy (β = 0.316, p=0.003) levels were independently associated with ω-6 FAs levels in the severe obese subjects. Vitamin B-12 was independently associated with ω-3 FAs (β = 0.251, p = 0.029) and ω-3/ω-6 ratio (β = 0.252, p=0.034) in the severe obese subjects. Also, tHcy (β = 0.316, p = 0.003) levels were independently associated

Table 3. Correlations of serum total cholesterol, TG, HDL-cholesterol and LDL-cholesterol with plasma ω-3 FAs, ω-6 FAs and the ω-3/ω-6 ratio of severe obese and normal weight subjects

	Control (n=65)			Obese (n=96)		
	ω-3 FAs	ω-6 FAs	ω-3/ω-6 ratio	ω-3 FAs	ω-6 FAs	ω-3/ω-6 ratio
Cholesterol	-0.075	0.319**	-0.193	-0.134	0.229*	-0.056
TG	0.054	0.095	0.082	0.093	0.137	0.049
HDL	0.151	0.122	-0.222	-0.077	0.128	-0.022
LDL	-0.160	0.264*	-0.137	-0.171	0.167	-0.089

ω-3 FAs, omega-3 fatty acids; ω-6 FAs, omega-6 fatty acids; TG, triglycerides; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; * $p< 0.05$; ** $p<0.01$

Table 4. Correlations of serum homocysteine with serum vitamin B_{12} and folic acid of severe obese and normal weight subjects

	Control (n=65)		Obese (n=96)	
	Vitamin B-12	Folic acid	Vitamin B-12	Folic acid
Homocysteine	-0.239*	-0.268*	-0.244*	-0.332**

* $p< 0.05$ ** $p< 0.01$

with ω-6 FAs (β = 0.380, p=0.001), ω-3 FAs (β = -0.506, p=0.001) and the ω-3/ω-6 ratio (β = 0.433, p=0.002) in the normal weight subjects (data not shown). But, tHcy, vitamin B-12 and folic acid were not independently associated with lipids and anthropometric measures. On the other hand, multiple linear regression analysis was performed to determine the independent association of lipids when controlled for ω-3 FAs, ω-6 FAs and ω-3/ω-6 ratio. The results showed that cholesterol was independently associated with the ω-6 FAs (β = 0.296, p=0.017) in the normal weight subjects (data not shown).

DISCUSSION

In the present study we have found no significant difference between plasma ω-3 FAs and ω-6 FAs levels of severe obese and normal weight subjects. However, there was a significantly negative correlation between ω-3 FAs and tHcy levels and a significantly positive correlation between ω-6 FAs and tHcy levels in both groups. This finding confirms that plasma ω-3 FAs have a protective effect against the development of CVD. Our finding is in accordance with the findings of Berstad *et al*.[17] who investigated healthy subjects and Pooya *et al*.[14] who investigated diabetic patients.

Dietary fish oil supplementation studies have shown conflicting results with respect to the effect of ω-3 FAs on plasma tHcy. Piolot *et al*.[20] found an increase in tHcy concentrations after fish-oil supplementation in healty subjects. In another study, Nenseter *et al.*[21] found that fish powder supplementation did not beneficially affect tHcy concentrations in hyperlipidemic subjects. However, Grundt *et al*.[22] and Olszewski *et al*.[23] observed reductions in tHcy concentrations in hyperlipidemic and cardiovascular disease patients supplemented with fish oil. Also, administration of fish oil was reported to be correlated with decreased tHcy concentrations in high risk populations, possibly reducing morbidity and mortality.[14,17] The results of these later studies also support our results. However, to our knowledge, our study is the first one performed on severe obese subjects.

Although the exact mechanism of this correlation is unknown, the high concentration of ω-3 FAs, specifically those of EPA and DHA, are reported to be the primary contributors.[15] Indeed, it has been reported that EPA and DHA effect lipid concentrations, the size and oxidizability of lipids, platelet aggregation, arrhythmias and endothelial activation.[15] It has been hypothesized that the effect of ω-3 FAs on tHcy metabolism could be due to modulation of gene expression in the enzyme or enzymes involved in the synthesis of tHcy.[17] For example, Huang *et al*.[24] reported that ω-3 FAs up-regulates cystathionine-g-lyase and 5-methyltetrahydrofolate reductase mRNA expression and down-regulates methionine adenosyltransferase mRNA expression involved in tHcy metabolism. They concluded that the regulatory effect of ω-3 FAs on critical gene expression was associated with decreased tHcy concentration. Altered ω-6/ω-3 FA balance was reported to result in increased tHcy levels.[25] Because, it was thought that an increase in dietary ω-6 FAs may lead to an increase in the production of prothrombotic rather than antithrombotic metabolites, increasing the risk of CVD.[26] Indeed, Kalogeropoulos *et al*.[26] have found that plasma ω-6/ω-3 ratio was positively associated with plasma tHcy levels in healthy subjects.

In this study, we found that tHcy levels of severe obese subjects were slightly but not significantly higher, whereas vitamin B-12 and folic acid levels were significantly lower than the same parameters of the normal weight subjects. Also, there was an inverse correlation of tHcy levels with vitamin B-12 and folic acid levels. There are conflicting findings in literature regarding tHcy, vitamin B-12 and folic acid levels in obese and normal weight subjects. For example, Vrentzos *et al*.[7] found negative correlation between serum vitamin B-12 and folic acid and tHcy concentrations in healthy subjects. This finding and those of some other investigators confirm our finding.[27,28]

However, Terruzzi *et al.*[29] and Brasileiro *et al.*[30] found no significant difference between plasma tHcy, vitamin B-12 and folic acid levels of obese and non-obese subjects.

Low serum folic acid and low vitamin B-12 levels are known to be predictors of plasma tHcy levels.[31] However, plasma tHcy levels of our severe obese subjects did not significantly changed in spite of decreased levels of vitamin B-12 and folic acid. The underlying mechanism of this findings is not known and needs to be investigated. However, epidemiologic studies have demonstrated that obese people replace fruit and vegetables with fatty foods.[32] Thus, lower serum folic acid and vitamin B_{12} levels in obese subjects than non-obese subjects may be due to habitual eating, genetic and autoimmune factors.

On the other hand, Brasileiro *et al.*[30] found no significant difference between tHcy and folic acid levels of obese and non-obese subjects. Also, Hirsch *et al.*[32] found that serum folic acid levels of obese females with non-alcoholic fatty liver was significantly lower than that of healthy controls, whereas there was no significant difference between tHcy and vitamin B-12 levels of the groups. Folic acid intake is recognized as the most significant dietary determinant of serum tHcy concentrations. There is a strong inverse relationship between dietary folic acid intake and serum tHcy concentrations. Increased serum folic acid levels lead to an increase in 5-methyltetrahydrofolate, which in turn increases the rate at which tHcy is remethylated to methionine, resulting in reduced serum tHcy levels.[7]

In conclusion, our results suggest significant associations between plasma ω-3 FAs and ω-6 FAs with serum tHcy concentrations and other significant risk factors in severe obese subjects. The mechanism which might explain the relationship between plasma ω-3 FAs and ω-6 FAs and serum tHcy levels is not yet clear and needs to be investigated. Our findings imply the importance of ω-3 fatty acids in the development of obesity related diseases in severe obese subjects.

AUTHOR DISCLOSURE

The authors stated that there are no conflicts of interest regarding the publication of this article.

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Original Article

Plasma ω-3 fatty acid levels negatively and ω-6 fatty acid levels positively associated with other cardiovascular risk factors including homocysteine in severe obese subjects

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重度肥胖者其血漿 ω-3 和 ω-6 脂肪酸與其他心血管危險因子包括同半胱胺酸成負向和正向相關

肥胖與同半胱胺酸皆是心血管疾病重要危險因子。血漿中 ω-3 和 ω-6 脂肪酸皆為必需脂肪酸，對人類健康和疾病卻有不同的生物學作用。本篇研究探討重度肥胖者其血漿 ω-3 和 ω-6 脂肪酸濃度與其他心血管危險因子包括同半胱胺酸之關聯。研究對象為 96 位重度肥胖及 65 位正常體重者，利用氣相層析質譜儀來測量血漿中脂肪酸組成；利用高壓液相層析儀來測定血清同半胱胺酸濃度。兩組之間的血清同半胱胺酸、血漿 ω-3 和 ω-6 脂肪酸濃度及其比值皆無顯著差異；然而，重度肥胖者的血清維生素 B-12(p<0.01)和葉酸(p<0.05)濃度較正常體重者低。兩組研究對象之同半胱胺酸皆與 ω-6 脂肪酸成正相關，與 ω-3 脂肪酸成負相關。重度肥胖者的血清維生素 B-12 與 ω-3 脂肪酸(p<0.01)、ω-3/ω-6 比值(p<0.01)成正相關，但與 ω-6 脂肪酸(p<0.05)成負相關。此外，重度肥胖者的血清葉酸亦與 ω-3 脂肪酸(p<0.01)成正相關。本研究結果顯示，重度肥胖與正常體重者，其血漿 ω-3 及 ω-6 脂肪酸皆與血清同半胱胺酸濃度具有相關性。低維生素 B-12 和葉酸濃度可能是使得重度肥胖者有較高同半胱胺酸濃度的原因，並提高未來罹患心血管疾病之風險。

關鍵字：ω-3 脂肪酸、ω-6 脂肪酸、同半胱胺酸、肥胖、維生素 B-12