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ORIGINAL ARTICLE

A hypertriglyceridemic state increases high sensitivity C-reactive protein of Japanese men with normal glucose tolerance

Kyoko Okada · Norihiro Furusyo · Masayuki Murata · Yasunori Sawayama · Mosaburo Kainuma · Jun Hayashi

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Abstract Both fasting and postprandial hypertriglyceridemia have been identified as risk markers for cardiovascular disease. High-sensitivity C-reactive protein (hs-CRP), known to independently predict future cardiovascular disease, has also been reported to be a direct participant in the progression of atherosclerosis. We evaluated whether or not fasting and/or postprandial hypertriglyceridemia influence hs-CRP of men with normal glucose tolerance. According to the triglyceride (TG) level, measured before and 1 and 2 h after a meal tolerance test, subjects were classified into a normotriglyceridemic (NTG) group ($n = 86$), a postprandial hypertriglyceridemia (PHTG) group ($n = 50$), or a fasting hypertriglyceridemia (FHTG) group ($n = 53$). Hs-CRP and HOMA-R were significantly higher in the FHTG group than in the other groups ($P < 0.01$). The PHTG group had higher hs-CRP than the NTG group ($P < 0.05$). No significant differences in age, BMI, LDL cholesterol, or carotid intima-media thickness were found in comparison of the three groups. Multivariate linear regression analysis showed that the area under the TG curve (AUC-TG), HbA1c, and BMI were independently correlated with hs-CRP ($P < 0.001$, $P = 0.016$, $P = 0.032$, respectively). Our data suggests that a hypertriglyceridemic state is associated with hs-CRP irrespective of BMI, LDL-C, and HDL-C, indicating that hs-CRP might represent chronic inflammation induced by hypertriglyceridemia in Japanese men with normal glucose tolerance.

Keywords High sensitivity C-reactive protein · Hypertriglyceridemia · Postprandial hypertriglyceridemia · Men with normal glucose tolerance

K. Okada (✉) · N. Furusyo · M. Murata · Y. Sawayama · M. Kainuma · J. Hayashi
Department of General Internal Medicine, Kyushu University Hospital, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: okyouko@gim.med.kyushu-u.ac.jp

N. Furusyo · M. Kainuma · J. Hayashi
Department of Environmental Medicine and Infectious Diseases, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

Introduction

Many epidemiological studies have reported associations between serum triglyceride concentrations and the risk of coronary heart disease (CHD) [1, 2], but their relevance to disease remains uncertain. One reason is that most focused on fasting levels of triglycerides, which excluded remnant lipoproteins. Increased levels of postprandial triglycerides indicate the presence of increased levels of remnant lipoprotein which not only activate surface molecules of monocytes and endothelial cells, but also induce foam cell formation and proliferation of smooth muscle cells [3]. Indeed, high levels of remnant-like particles cholesterol (RLP-C) are considered to be a coronary risk factor and a predictor of cardiovascular events, independent of both high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) in healthy subjects and patients with coronary artery disease (CAD) [4].

Atherosclerosis is fundamentally an inflammatory disease in which high sensitivity C-reactive protein (hs-CRP), an inflammatory biomarker, is associated with a markedly increased risk of cardiovascular disease, stroke, peripheral arterial disease, and sudden cardiac death, even among apparently healthy individuals with low levels of LDL [5, 6]. As of now, more than a dozen large-scale studies have demonstrated in aggregate that hs-CRP levels are a strong

independent predictor of future vascular events and that hs-CRP adds prognostic information on risk at all levels of LDL, at all levels of the Framingham risk score, and at all levels of the metabolic syndrome [7]. However, to our knowledge, no report has evaluated the association between hs-CRP and the area under the triglyceride curve after a meal tolerance test.

We examined the hypothesis that fasting and/or a postprandial hypertriglyceridemia state influences hs-CRP of men with normal glucose tolerance.

Methods

Study subjects

A total of 203 consecutive male patients (mean age 49.3 ± 14.5 years; range 22–78 years) were recruited at the outpatient clinic of the Department of General Internal Medicine, Kyushu University, from March 2006 to December 2009. The examination consisted of a questionnaire, general physical question, blood tests, carotid ultrasound, and a cookie test. Eligibility criteria included (a) men from 20 to 79 years; (b) BMI (body mass index) <30 kg/m^2; (c) fasting plasma glucose (PG) <110 mg/dl; (d) PG <140 mg/dl at 2 h after the meal test; (e) hemoglobin A1c (HbA1c) <6.5%. Exclusion criteria were a clinical history and/or evidence of diabetes, preexisting heart disease, renal insufficiency, endocrine disease, liver disease, cancer, or history of chronic use of medications, such as glucocorticoids, that could affect the hs-CRP or lipid determinations. Of the potential subjects, fourteen patients were omitted because of withdrawal of consent or ineligibility, leaving the data of 189 available for analysis. The 189 subjects were divided into three groups according to the results of the cookie test [8–10]: (1) a normotriglyceridemic group (NTG) ($n = 86$), which consists of both fasting serum triglyceride (TG) level <150 mg/dl and TG change from 0 to 120 min <66 mg/dl; (2) a postprandial hypertriglyceridemic group (PHTG) ($n = 50$), fasting TG level <150 mg/dl, and TG change from 0 to 60 or 120 min ≥66 mg/dl; and (3) a fasting hypertriglyceridemic group (FHTG) ($n = 53$), fasting TG level ≥150 mg/dl. Hypertension was defined as either mean systolic blood pressure ≥140 mmHg, mean diastolic blood pressure ≥90 mmHg, or treatment with antihypertensive medications. Hyperlipidemia was defined as either low-density lipoprotein cholesterol (LDL) ≥140 mg/dl, TG ≥150 mg/dl, or lipid-lowering drug administration. Written informed consent was obtained from each participant before testing. The study protocol was reviewed and approved by the Ethic Committee of Kyushu University Hospital.

Cookie test

After a 10–14 h overnight fast, a cookie test was done by all patients between 8:30 and 9:30 AM. Ingested within 15 min, the test meal was a cookie (Saraya Co., Ltd., Osaka, Japan), consisting of the following: energy 592 kcal; carbohydrate 75 g; protein 8 g; and fat 28.5 g [8–10]. The amount of carbohydrate in this cookie is equivalent to that (75 g) in the standard oral glucose tolerance test (OGTT) (Trelan-G, Shimizu Pharmaceutical, Shimizu, Japan). Patients were asked not to do any unusual exercise or drink alcohol the day before the test. During the test, water was allowed, but no other beverages or foods were permitted. Blood samples were taken at 0, 60, 120 min for the measurement of PG, immunoreactive insulin (IRI), and TG, at 0 and 120 min for TC, high-density lipoprotein cholesterol (HDL), and remnant-like lipoprotein cholesterol (RLP-C). Samples were taken in a fasting state for LDL, apolipoprotein B (ApoB), high-sensitivity CRP (hs-CRP), and hemoglobinA1c (HbA1c).

Biochemical measurements

PG was measured by glucose oxidase method. IRI and C-peptide were measured by radioimmunoassay at a commercial laboratory (MBC Laboratories, Inc., Tokyo, Japan). HbA1c levels were measured by high-pressure liquid chromatography. The value for HbA1c (%) is estimated as an NGSP (National Glycohemoglobin Standaridization Program) equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS) (Japan Diabetes Society) (%) + 0.4% [11]. Serum TC, HDL, and TG were all measured enzymatically. LDL was determined directly at the above laboratory. Hs-CRP was measured by high sensitivity latex-enhanced immunonephelometics. ApoB was measured by turbidimetric immunoassay. RLP-C was measured by agarose gel electrophoresis.

Carotid ultrasound measurement

Trained and certified physicians scanned the carotid arteries bilaterally with high-resolution B-mode ultrasound using a 7.5 MHz mechanical sector transducer on the Aloka SSD-2000 (Aloka co., Ltd., Tokyo, Japan). Carotid IMT was measured at points 2, 2.5, and 3 cm proximal to the flow divider on the far wall of the right and left common carotid arteries at the end of the diastolic phase [12]. From this, mean IMT was determined for each individual.

Statistical analysis

Insulin resistance was estimated by homeostasis model assessment (HOMA-IR), calculated as fasting PG

(mg/dl) × fasting IRI (μU/ml)/405 [13]. The area under the curve (AUC) during the meal test was estimated by the linear trapezoidal method. Data are expressed as the mean value ± SD or number (%) of patients. Skewed variables were log-transformed before analyses. Differences in the means of continuous measurements between groups were calculated using ANOVA and post hoc analyses (Bonferroni method). Categorical variables among the groups were assessed using the χ^2 test. Associations between hs-CRP and variables were determined by calculation of Pearson correlation coefficients. The assessment of independent risk factors for hs-CRP was performed by multivariate linear regression analysis using the independent variables that had a significant correlation with hs-CRP in univariate linear regression analysis. Because of multicollinearity among TC, LDL, and ApoB, and among AUC-TG, AUC-RLP-C, TG 0, 60, and 120 min, we chose ApoB, and AUC-TG for explanatory variables. A P value <0.05 was considered to indicate statistical significance; all tests were two-tailed. All statistical analyses were performed on a personal computer with the statistical package SPSS for Windows (PASW Statistics 18).

Results

The characteristics of the subjects are summarized in Table 1. No significant differences in age, blood pressure, BMI, medical history, LDL, plasma glucose, IRI, HbA1c, or IMT were found between the three groups. The TC level was significantly higher in the FHTG group than in the NTG and PHTG groups ($P < 0.001$ and $P = 0.02$, respectively). No significant difference in TC level was found between the NTG and PHTG groups. TG, ApoB, and RLP-C levels were significantly higher in FHTG group than in both NTG and PHTG group ($P < 0.001$, respectively). HDL level were significantly lower in FHTG group than in both NTG and PHTG group ($P < 0.001$, respectively). No significant difference in HDL, TG, ApoB, or RLP-C level was found between the NTG and PHTG groups. HOMA-IR was significantly higher in the FHTG group than in the NTG group ($P = 0.007$).

Figure 1a, b shows the change and the area under the curves of TG and RLP-C in response to the cookie test. AUC-TG was significantly higher in the FHTG group than in the NTG and PHTG groups ($P < 0.001$, respectively). AUC-TG was significantly higher in the PHTG group than in the NTG group ($P < 0.001$). AUC-RLP-C was significantly higher in the FHTG group than in the NTG and PHTG groups ($P < 0.001$, respectively). AUC-RLP-C was significantly higher in the PHTG group than in the NTG group ($P < 0.05$). Figure 1c–e shows the change and the area under the curves of TC, HDL, and ApoB levels in response to the cookie test. TC levels were not significantly different between the three groups in either the fasting or the postprandial state. AUC-HDL was significantly lower in the FHTG group than in the NTG and PHTG groups ($P < 0.001$). AUC-ApoB was significantly higher in the FHTG group than in the NTG and PHTG groups ($P < 0.001$). Between the NTG and PHTG groups, no significant difference was found in AUC-HDL or AUC-ApoB. Figure 1f, g shows the change and the area under the curves of plasma glucose and IRI in response to the meal test. Neither fasting nor postprandial glucose levels were significantly different between the three groups. AUC-IRI was significantly higher in the FHTG group than in the NTG and PHTG groups ($P < 0.01$ and $P < 0.05$, respectively). No difference in AUC-IRI level was found in the NTG and PHTG groups.

Figure 2 shows hs-CRP levels between the three groups. Hs-CRP levels was significantly higher in FHTG group (0.139 ± 0.020 mg/dl) than in PHTG (0.073 ± 0.011 mg/dl) group and NTG (0.037 ± 0.003 mg/dl) group ($P < 0.01$, respectively). Hs-CRP levels was also significantly higher in PHTG group than in NTG group ($P < 0.05$).

Table 2 shows that univariate and multivariate regression analysis using hs-CRP as a dependent variable showed that AUC-TG, HbA1c, and BMI were independently correlated with hs-CRP ($P < 0.001$, $P = 0.016$, $P = 0.032$, respectively) after adjusting for age, blood pressure, HOMA-IR, ApoB, plasma glucose, IRI, and IMT.

Discussion

In this study, we found that hs-CRP levels were higher in a hypertriglyceridemic group than in a normal triglyceride group of men with normal glucose tolerance. Multivariate logistic analysis revealed that this association remained significant after adjustment for risk factors for atherosclerosis.

Previous epidemiologic studies have shown a significant association between elevated serum concentrations of CRP and the prevalence of underlying atherosclerosis [5, 6] and the incidence of first or recurrent cardiovascular events among individuals at risk for atherosclerosis [14]. In addition, Ridker et al. [15] revealed that rosuvastatin prevented vascular events and ischemic stroke with elevated hs-CRP by reducing hs-CRP regardless of LDL-C level. Therefore, it would seem that to improve the inflammatory state, that is to decrease the hs-CRP level, might provide a beneficial effect for atherosclerotic disease patients and reduce the mortality rate for those at risk.

Although the contribution of triglyceride to cardiovascular risk has been debated in the past, it now seems clear

Table 1 Characteristics of the study groups

	NTG ($n = 86$)	PHTG ($n = 50$)	FHTG ($n = 53$)	P value	NTG vs. PHTG (P value)	NTG vs. FHTG (P value)	PHTG vs. FHTG (P value)
Age (years)	49.9 ± 14.0	49.3 ± 15.5	48.5 ± 14.7	0.864	0.832	0.589	0.774
Blood pressure (mmHg)							
Systolic	126.8 ± 18.4	125.3 ± 15.1	125.9 ± 17.0	0.921	0.714	0.751	0.954
Diastolic	79.4 ± 12.5	78.1 ± 10.2	79.1 ± 11.4	0.958	0.774	0.854	0.917
BMI (kg/m^2)	23.9 ± 4.5	23.6 ± 3.1	25.0 ± 3.3	0.140	0.709	0.109	0.068
Medical history							
Hypertension	28 (32.6)	12 (24.0)	16 (30.2)	0.571	0.771	0.291	0.481
Therapy for hypertension	25 (29.1)	12 (24.0)	14 (26.4)	0.452	0.837	0.421	0.572
Dyslipidemia	21 (24.4)	17 (34.0)	20 (37.7)	0.088	0.094	0.956	0.693
Therapy for dyslipidemia	11 (12.8)	8 (16.0)	10 (18.9)	0.663	0.103	0.987	0.778
Diabetes mellitus	0 (0)	0 (0)	0 (0)	–	–	–	–
Cardiovascular disease	2 (2.3)	0 (0)	3 (5.7)	0.196	0.305	0.277	0.088
Cerebral vascular disease	2 (2.3)	0 (0)	3 (5.7)	0.196	0.305	0.277	0.088
Serum lipids							
TC (mg/dl)	183.3 ± 42.8	192.3 ± 32.3	210.1 ± 36.4	<0.001	0.191	<0.001	0.020
LDL (mg/dl)	113.7 ± 38.4	120.6 ± 27.4	120.8 ± 31.6	0.385	0.138	0.168	0.890
HDL (mg/dl)	50.9 ± 12.2	50.9 ± 14.1	42.0 ± 10.6	<0.001	0.993	<0.001	<0.001
TG (mg/dl)	93.7 ± 25.9	105.9 ± 24.5	236.3 ± 111.3	<0.001	0.301	<0.001	<0.001
ApoB (mg/dl)	85.5 ± 26.4	93.3 ± 17.4	109.6 ± 20.3	<0.001	0.055	<0.001	<0.001
RLP-C (mg/dl)	4.51 ± 1.93	4.95 ± 1.72	12.6 ± 9.61	<0.001	0.656	<0.001	<0.001
Plasma glucose (mg/dl)	93.6 ± 8.3	94.5 ± 11.0	95.9 ± 8.9	0.587	0.499	0.308	0.666
IRI (μU/ml)	7.3 ± 3.7	9.9 ± 12.9	13.7 ± 9.0	0.057	0.577	0.068	0.086
HbA1c (%)	5.9 ± 0.8	6.0 ± 0.8	5.9 ± 0.8	0.579	0.368	0.406	0.923
HOMA-IR	1.7 ± 1.4	1.9 ± 2.3	2.5 ± 1.6	0.026	0.484	0.007	0.084
IMT (mm)	0.72 ± 0.13	0.71 ± 0.14	0.75 ± 0.13	0.167	0.554	0.322	0.192

Data represents as the mean value ± SD or number (%) of patients. P value is calculated by ANOVA and χ^2 test for three groups and by Bonferroni for two groups

BMI body mass index, *TC* total cholesterol, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *ApoB* apolipoprotein B, *RLP-C* remnant lipoprotein cholesterol, *IRI* immuno-reactive insulin, *HOMA-IR* homeostasis model assessment of insulin resistance, *IMT* intima-media thickness, *HbA1c* hemoglobin A1c is estimated as an NGSP equivalent value (%) calculated by the formula HbA1c (%) = HBA1c (JDS) (%) + 0.4%

that elevated triglyceride levels are independently associated with cardiovascular risk, particularly coronary risk [16]. It remains uncertain, however, whether this association is causal, such that hypertriglyceridemia causes atherosclerosis [17, 18]. Indeed, other studies have found higher TG levels in adults in the general population is predictive of future cardiovascular disease. To our knowledge, this is the first report showing that hs-CRP is associated with the TG level of men with normal glucose tolerance.

Increased levels of triglycerides indicate the presence of increased levels of remnants from chylomicrons and very low-density lipoproteins [3]. Some researchers reported that these cholesterol-containing, triglyceride-rich lipoproteins penetrate the arterial endothelium, potentially leading to the development of atherosclerosis [19, 20]. In our study, carotid IMT levels among the three groups were not significantly different. In contrast, Teno et al. [21] showed that carotid IMT was increased in diabetic patients with both postprandial and fasting hypertriglyceridemia, and that postprandial TG levels showed the strongest influence on carotid IMT. The reason for this difference might be that in our study diabetic and/or borderline type patients were excluded, so that carotid atherosclerosis had not progressed as far.

Hs-CRP levels vary remarkably by race and ethnic group. Previous Japanese study revealed that the hs-CRP levels of Japanese were much lower than those of Western

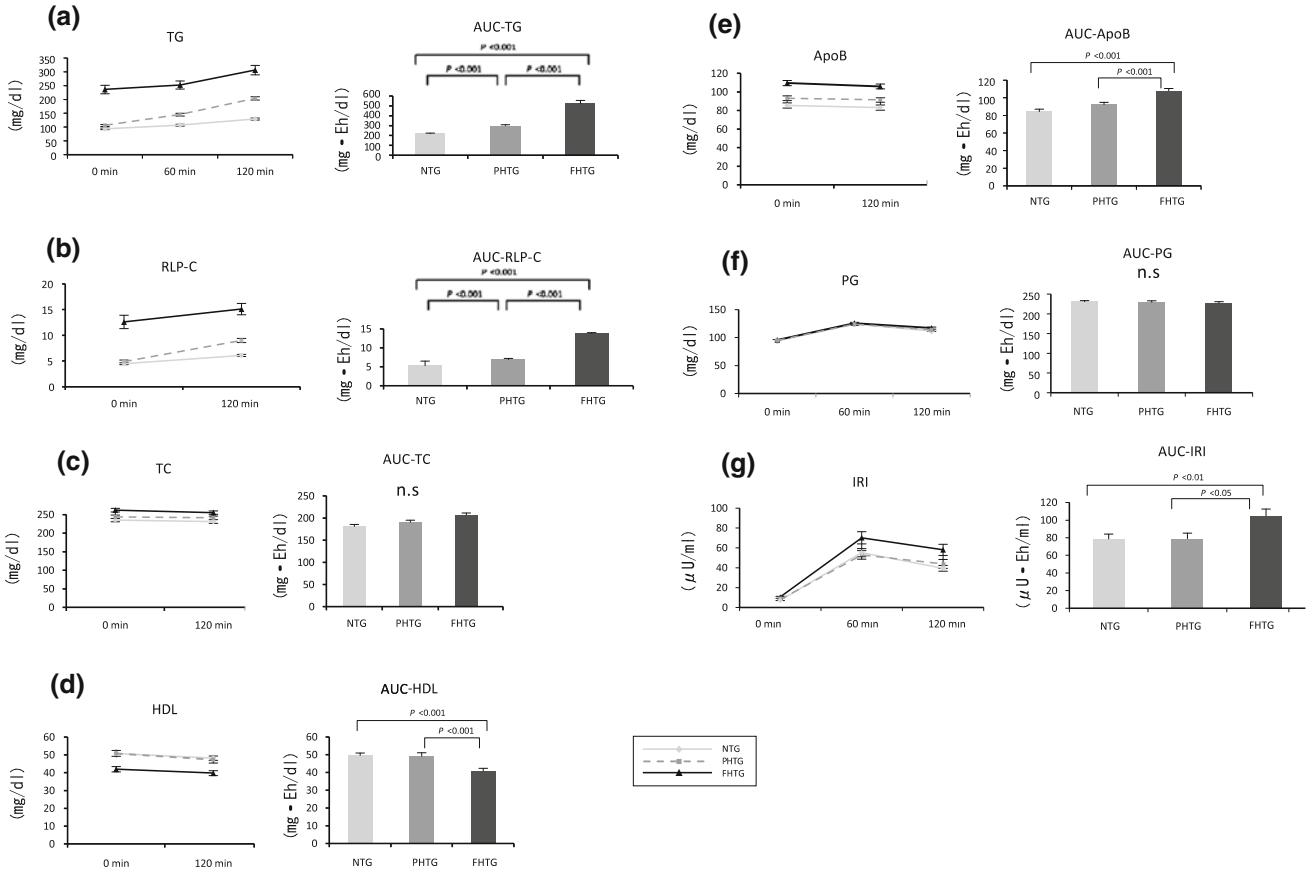

Fig. 1 The 2-h course of TG (**a**), RLP-C (**b**), TC (**c**), HDL (**d**), ApoB (**e**), PG (**f**), and IRI (**g**) concentrations after cookie test in NTG (*white diamond*), PHTG (*gray square*), and FHTG (*black triangle*). Bars (*white*, NTG; *gray*, PHTG; *black*, FHTG) in the *insets* represent respective 2 h-AUC values. *PG* plasma glucose, *IRI* immunoreactive insulin, *TC* total cholesterol, *HDL* high-density lipoprotein cholesterol, *TG* serum triglyceride, *RLP-C* remnant-lipoprotein cholesterol, *NTG* normotriglyceridemic group, *PHTG* postprandial hypertriglyceridemic group, *FHTG* fasting hypertriglyceridemic group. Data represents mean ± SE

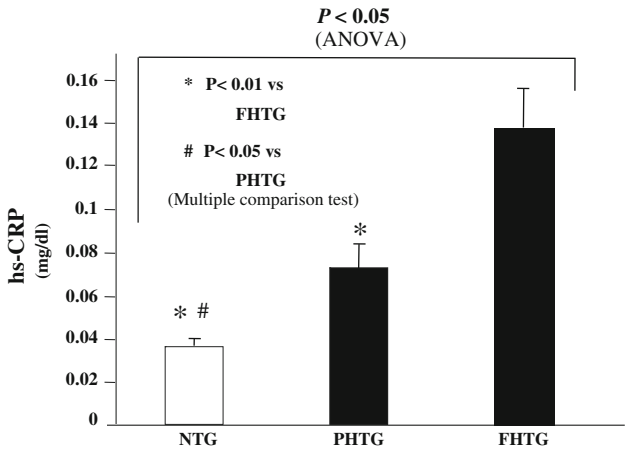

Fig. 2 Comparison of serum levels of hs-CRP among the three groups. *Hs-CRP* high-sensitivity C-reactive protein, *NTG* normotriglyceridemic group, *PHTG* postprandial hypertriglyceridemic group, *FHTG* fasting hypertriglyceridemic group. Data represents mean ± SE

populations (median 0.043 mg/dl vs. 0.20 mg/dl) [22–24]; however, the association between hs-CRP level and CHD was continuous from very low hs-CRP levels, and it was revealed that a slightly elevated hs-CRP level of more than 0.1 mg/dl was clearly associated with an increased risk of a future coronary event [22]. In our study, as in previous Japanese study, the hs-CRP levels in the NTG group were relatively low. However, the hs-levels increased continuously in the PHTG group and the FHTG group, significantly, irrespective of BMI, LDL-C, and HDL-C. It is reasonable to suppose that the hypertriglyceridemic state might increase hs-CRP.

Epidemiological studies indicate that consumption of the highly processed, calorie-dense, nutrient-poor diet favored in the Western World leads to exaggerated postprandial hypertriglyceridemia, as does low physical activity [25]. Thus, nonpharmacologic interventions that involve aggressive lifestyle modification, such as hypocaloric Mediterranean diet and adequate physical activity, should be the first line therapy [26, 27].

Table 2 Univariate and multivariate linear regression analysis using hs-CRP as dependent variable

	Univariate analysis		Multivariate analysis	
	r	*P* value	Standardized regression coefficient	*P* value
AUC-TG	0.301	<0.001	0.270	<0.001
ApoB				
0 min	0.283	<0.001		
BMI	0.238	0.003	0.206	0.032
HbA1c	0.227	0.01	0.229	0.016
Age	0.023	0.760		
Blood pressure				
Systolic	0.032	0.738		
Diastolic	0.025	0.788		
HOMA-IR	0.078	0.288		
TC				
0 min	0.200	0.006		
LDL				
0 min	0.147	0.043		
HDL				
0 min	−0.125	0.043		
TG				
0 min	0.299	<0.001		
60 min	0.298	<0.001		
120 min	0.290	<0.001		
Plasma glucose				
0 min	0.071	0.332		
60 min	−0.031	0.674		
120 min	0.129	0.077		
IRI				
0 min	0.076	0.299		
60 min	−0.028	0.699		
120 min	0.077	0.294		
Intima-media thickness	0.071	0.508		

Abbreviations as in Table 1

Limitations of our study are that hs-CRP and lipid parameters were measured only once, and thus could reflect random fluctuations and intra-individual variations. Furthermore, subclinical infection could cause elevations in hs-CRP, which would increase the variability in this measure. Because of the cross-sectional design of the study, we cannot infer from our results a cause-and-effect relationship between hs-CRP and hypertriglyceridemia. We hypothesize that inflammation and dyslipidemia cluster. Longitudinal tracking of lipid levels, as well as their temporal relationship to inflammatory markers are needed.

In conclusion, the serum hs-CRP level was shown to be closely associated with the hypertriglyceride status of men with normal glucose tolerance.

Conflict of interest None.

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