Is there any relationship between coronary artery disease and postprandial triglyceride levels?

Koroner arter hastalığı ve tokluk trigliserid düzeyleri arasında herhangi bir ilişki var mıdır?

İnci Aslı Atar, İlyas Atar[1], Alp Aydınalp[1], Çağatay Ertan[1], Hüseyin Bozbaş[1], Bülent Özin[1], Aylin Yıldırır[1], Haldun Müderrisoğlu[1]

Cardiology Clinic, Güven Hospital, Ankara
[1]Department of Cardiology, Faculty of Medicine, Başkent University, Ankara, Turkey

Abstract

Objective: We aimed to evaluate the relationship between postprandial triglyceride (PPTG) levels and coronary artery disease (CAD).
Methods: A total of 80 patients were included in this prospective cohort study. Oral lipid loading was used in order to measure PPTG levels. In the fasting state and after the high fat breakfast, triglyceride levels were measured by enzymatic methods at 2nd, 4th, 6th and 8th hours. We made subgroup analysis to show the effects of lipid loading on triglyceride levels in patients with and without fasting hypertriglyceridemia. We evaluated triglyceride levels and changes of triglyceride levels in percentages after lipid loading using a general linear model for repeated measures. Sample size analysis was performed.
Results: Baseline clinical, demographic and laboratory characteristics of both groups were similar. The peak triglyceride levels were seen at the 4th hour in both groups. Triglyceride levels were significantly increased after lipid-rich-breakfast loading compared to baseline levels in both groups ($p<0.001$) but these changes were not significant ($p=0.279$). In patients with elevated fasting triglyceride levels, the area under the plasma triglyceride concentration curve was significantly larger in CAD group than control group (334±103 vs. 233±58 mg/dl, $p=0.02$).
Conclusion: Our data show that in patients who have a high fasting triglyceride level, high levels of PPTG may be related to CAD, however high PPTG levels are not related to CAD in patients with normal fasting levels of triglyceride.
(Anadolu Kardiyol Derg 2011; 11: 201-6)
Key words: Coronary artery disease, postprandial triglyceride, lipid loading, hypertriglyceridemia

ÖZET

Amaç: Biz bu çalışmada, tokluk trigliserid (TTG) düzeyi ve koroner arter hastalığı (KAH) arasındaki ilişkiyi araştırmayı amaçladık.
Yöntemler: Bu prospektif kohort çalışmasına toplam 80 hasta dahil edildi ve TTG düzeyini ölçmek için ağızdan lipit yüklemesi yapıldı. Aç olarak ve lipitten zengin bir kahvaltı sonrası 2., 4., 6. ve 8. saatte tok olarak trigliserid düzeyi enzimatik yöntemle ölçüldü. Açlık trigliserid yüksekliği olan ve olmayan bireylerde lipit yüklemesinin trigliserid düzeyi üzerine etkisinin değerlendirilmesi için alt grup analizi uygulandı. Lipid yüklemesi sonrası trigliserid düzeyleri ve trigliserid düzeyindeki yüzde değişim oranları "tekrarlayan değerler için genel lineer model" analizi ile değerlendirildi. Örneklem büyüklüğü hesaplandı.
Bulgular: Başlangıçtaki klinik, demografik ve biyokimyasal ölçümlerin sonuçları gruplar arasında benzerdi. Her iki grupta da zirve trigliserid seviyesi lipit yüklemesi sonrası 4. saatteydi. Lipit yüklemesi sonrası her iki grupta da trigliserid düzeyleri başlangıca göre anlamlı olarak arttı ($p<0.001$) ancak bu değişimler iki grup arasında farklı değildi ($p=0.279$). Alt grup analizlerinde; açlık trigliserid yüksekliği olan alt grupta, trigliserid düzeyi eğrisi altında kalan alanda KAH grubunda kontrol grubuna göre anlamlı yükseklik vardı (334±103 vs. 233±58 mg/dl, $p=0.02$).
Sonuç: Bizim sonuçlarımız, açlık trigliserid düzeyi yüksek olan hastalarda TTG yüksekliğinin KAH ile ilişkili olabileceğini, ancak açlık trigliserid düzeyi yüksek olmayan hastalarda TTG düzeyi ile KAH arasında bir ilişki olmadığını göstermektedir.
(Anadolu Kardiyol Derg 2011; 11: 201-6)
Anahtar kelimeler: Koroner arter hastalığı, tokluk trigliserid, lipit yüklemesi, hipertrigliseridemi

Address for Correspondence/Yazışma Adresi: Dr. İlyas Atar, Department of Cardiology, Faculty of Medicine, Başkent University, 1. Cad. 10. Sok. Bahçelievler 06490 Ankara, Turkey Phone: +90 312 212 68 68 Fax: +90 312 223 73 33 E-mail: ilyasatar@gmail.com

Accepted Date/Kabul Tarihi: 25.01.2011 **Available Online Date/Çevrimiçi Yayın Tarihi:** 21.03.2011

doi:10.5152/akd.2011.053

Introduction

The relationship between hypertriglyceridemia and the risk for coronary artery disease (CAD) has been an issue of great interest and controversy. Hypertriglyceridemia is a heterogeneous disorder and some prospective epidemiological studies have reported a positive relationship between serum fasting triglyceride levels and CAD, however hypertriglyceridemia as an independent risk factor for CAD is still controversial (1-3). Hypertriglyceridemia correlates strongly with the presence of small, dense particles of low-density lipoprotein (LDL) cholesterol and reductions of high-density lipoprotein (HDL) cholesterol, both of which are known to be associated with premature CAD (4, 5).

Triglycerides are usually measured in the fasting state at the lowest triglyceride level of the day according to the guidelines (6). Postprandial hypertriglyceridemia, reflecting an elevated concentration of lipoprotein remnant particles, might change atherosclerotic lesion content and might show procoagulant, anti-fibrinolytic and pro-inflammatory effects (7, 8). Previously some prospective studies (9-16) and case-control studies (17-21) demonstrated a relationship between nonfasting triglyceride levels and cardiovascular disease. These case-control studies used different fat loading protocols in different patient groups and conflicting results were found.

In this study, we aimed to evaluate if there is any relation between postprandial triglyceride (PPTG) levels and CAD using a specific triglyceride loading protocol and serial biochemical analysis for measurement of triglyceride levels in the selected patient groups.

Methods

Patients and study protocol

A total of 152 patients who had undergone coronary angiography were screened and 80 patients who didn't have any exclusion criteria were included in this prospective cohort study. Forty patients who had CAD were included in the CAD group. CAD was diagnosed with coronary angiography and at least one of the below mentioned criteria were required to make the diagnosis: a stenosis of more than 50% in an epicardial coronary artery, a history of percutaneous coronary intervention or coronary artery bypass graft surgery, a history of myocardial infarction with a stenotic lesion in an epicardial coronary artery. In CAD group none of the patients had acute coronary syndromes.

Forty subjects with matching baseline clinical, demographical and laboratory characteristics with a maximum stenosis of 20% in any of the epicardial coronary arteries and without overt coronary artery disease were included in the control group.

The mean age of the study population was 59.4±10.1 years and 17 of them were females. Patients who were on lipid lowering therapy for a period of 6 weeks before the beginning of the study and who had the following conditions were excluded from the study: fasting triglyceride levels higher than 400 mg/dL, chronic renal and hepatic diseases, diabetes mellitus, acute or chronic pancreatitis, connective tissue disorders, hypothyroidism, malabsorption syndromes, enteropathies and acute coronary syndromes.

The research protocol was approved by the Başkent University Ethics Committee. Informed consent was obtained for all patients.

According to the guidelines normal triglyceride levels are below 150 mg/dL (6). A high fasting triglyceride level (hypertriglyceridemia) is defined as a fasting triglyceride level of >150 mg/dL. A high PPTG level is defined as a level above 150 mg/dL in any of the measurements after lipid loading.

Lipid loading protocol

Oral lipid loading was used in order to measure PPTG levels. Lipid enriched enteral solutions or meals with a high fat and caloric content are used for lipid loading in literature (17-21). Since it is well tolerated by the patients and easily provided in our country we preferred to give a breakfast rich in lipids. All subjects received a breakfast consisting 60% of fat, 16.8% of protein and 23.2% of carbohydrates, with a total of 891 kcal. The breakfast was ordered with a dietitian and the detailed contents of the breakfast are shown in Table 1. The patients consumed all of the breakfast and did not eat anything else during the 8 hours after ingestion. All the procedures (having breakfast, obtaining blood samples, etc) were performed during the hospitalization of the patients and were confirmed by the medical staff for each participant. All subjects tolerated the meal well and none had diarrhea or other symptoms of malabsorption.

Biochemical analyses

Before the ingestion of the lipid rich breakfast a baseline fasting blood sample was collected from each patient to measure baseline levels of glucose, total cholesterol, LDL, HDL, and triglyceride after 12 hours fasting state. After the lipid rich breakfast, measurement of triglyceride levels were repeated at 2nd, 4th, 6th and 8th hours. Serum triglyceride measurements were done by enzymatic colorimetric method (PP Moduler autoanalyzer, Roche Diagnostics GmbH, Germany).

Table 1. The details of the breakfast given to the patients

Nutrients	Protein, gr	Lipids, gr	Carbohydrates, gr	Energy, kcal
Cheese (60 gr)	16.2	19.2	0.84	242
Milk (200 cc)	6.6	6.6	9.4	122
Eggs (50 gr)	6.05	5.6	0.6	79
Butter (15 gr)	0.135	12.165	0.015	107.5
Walnuts (15 gr)	2.22	9.6	2.37	92.25
Bread (75 gr)	6.08	0.6	42.3	207
Olives (15 gr)	0.36	4.2	0.22	41.4
Total, gr (%)	37.6 (16.8)	57.9 (60)	55.7 (23.2)	891
Categorical variables are expressed as number (percentage)				

Statistical analyses

The statistical package SPSS (Statistical Package for the Social Sciences, version 9.0, SSPS Inc, Chicago, Ill, USA) was used for statistical analyses.

Continuous variables are expressed as means±standard deviation (median). All continuous variables were checked with Kolmogorov-Smirnov normality test to show their distributions. Continuous variables with normal distributions were compared using the unpaired Student t-test. Continuous variables with abnormal distributions were compared using the Mann-Whitney U test. The changes of triglyceride levels compared to the basal values were calculated in percentages and these percentages were compared using the Mann-Whitney U test. For categorical variables, the Chi-square test was used.

We made subgroup analysis to show the effects of lipid loading on triglyceride levels in patients with and without fasting hypertriglyceridemia. Patients were divided into two subgroups according to their fasting triglyceride levels. According to baseline triglyceride levels 21 patients (26.2%) [11 (27.5%) patients in CAD group and 10 (25%) patients in control group, p=1.0] had hypertriglyceridemia and 59 patients (73.8%) did not have hypertriglyceridemia (6). Fasting and PPTG levels and PPTG changes in percentages compared to baseline fasting levels were analyzed using the Mann-Whitney U test in these subgroups.

Areas under the curves were calculated for each patient and the Mann-Whitney U test used to detect differences between the groups and subgroups (22). We used a general linear model for repeated measures (ANOVA) to evaluate triglyceride levels and changes of triglyceride levels in percentages after lipid loading in main data and subgroup analysis. Tukey and Duncan tests were used for posthoc analyses. P values of less than 0.05 were considered statistically significant for all tests.

Sample size calculation: Power analysis was performed for the triglyceride levels data for the patient groups with and without coronary artery disease. To obtain a precision of 10% at a type I error level of 5% with 80% power, the required sample size was found to be 64. In view of potential losses for technical reasons, the study was planned to enroll at least 80 subjects.

Results

Main data results

Baseline clinical and demographic characteristics of both groups were similar (Table 2). Total cholesterol, LDL cholesterol and HDL cholesterol levels were similar in the two groups (Table 2). Baseline triglyceride levels were higher in CAD group than control group but this difference was not significant (Table 3). After fat loading 51 patients (63.7%) (25, 62.5% patients in CAD group and 26, 65% patients in control group, p=0.815) had hypertriglyceridemia.

Mean triglyceride levels in the CAD group at the 2nd, 4th, 6th and 8th hours after fat loading were higher than those in the control group; however, this difference was not statistically significant (Table 3). The peak triglyceride levels were seen at the 4th hour in both groups. In the control group triglyceride levels decreased to baseline levels at the 8th hour but in the CAD group triglyceride levels were still minimally higher than baseline levels at the 8th hour. The areas under the plasma triglyceride concentration curves in the two groups were similar (Table 3). In general linear model analysis, triglyceride levels were significantly increased after fat loading compared to baseline triglyc-

Table 2. Baseline clinical, demographical and laboratory characteristics of patients

Variables	CAD group (n=40)	Control group (n=40)	p*
Age, years	59.9±9.1 (59)	59.0±11.0 (62)	0.676
Sex, female, n (%)	8 (20)	9 (22)	1.0
Body mass index, kg/m^2	27.6±4.1 (27.6)	26.5±4.6 (25.8)	0.264
Hypertension, n (%)	28 (70)	20 (50)	0.110
Smoking, n (%)	22 (55)	22 (55)	1.0
Family history of CAD, n (%)	17 (42)	11 (27)	0.241
Sedentary life style, n (%)	27 (67)	22 (55)	0.359
Fasting glucose levels, mg/dL	95.3±25.7 (90)	89.2±14.3 (86)	0.134
Creatinine, mg/dL	1.0±0.3 (1.0)	1.0±0.2 (1.0)	0.955
ALT (U/L)	19.1±8.2 (18)	21.9±10.2 (19)	0.289
Hemoglobin, gr/dL	14.0±1.2 (14.0)	13.8±1.2 (13.8)	0.810
Total cholesterol, mg/dL	187±38 (188)	184±31 (179)	0.658
LDL cholesterol, mg/dL	117±31 (112)	114±24 (109)	0.625
HDL cholesterol, mg/dL	39±10 (38)	41±11 (40)	0.397

Continuous variables are expressed as means±standard deviation (median) and categorical variables are expressed as number (percentage)
*unpaired Student t-test, Mann-Whitney U test and Chi-square test
ALT - alanine aminotransferase, CAD - coronary artery disease, HDL - high-density lipoprotein, LDL - low-density lipoprotein

Table 3. Fasting and postprandial triglyceride levels for CAD patients and controls

Variables	CAD group (n=40)	Control group (n=40)	p*
Baseline TG levels, mg/dL	136±76 (106)	121±59 (107)	0.614
TG levels at 2nd hour, mg/dL	191±116 (149)	159±57 (162)	0.795
Percent change at the 2nd hour, %**	+41	+39	0.816
TG levels at 4th hour, mg/dL	211±138 (163)	178±80 (168)	0.830
Percent change at the 4th hour, %**	+54	+52	0.776
TG levels at the 6th hour, mg/dL	188±130 (155)	151±81 (135)	0.261
Percent change at the 6th hour, %**	+39	+26	0.135
TG levels at the 8th hour, mg/dL	146±95 (122)	122±67 (100)	0.334
Percent change at the 8th hour, %**	+8	+2	0.349
Area under TG curve, mg/dL.h	186±118 (141)	154±66 (146)	0.652

Continuous variables are expressed as means±standard deviation (median)
*unpaired Student t-test and Mann-Whitney U test
CAD - coronary artery disease, TG - triglyceride
**Postprandial change in triglyceride levels compared to baseline triglyceride levels

eride levels in both groups (F=231.197; p<0.001) but this change was not significantly different between the two groups (F=1.939; p=0.168). Percent changes of triglyceride levels in the postprandial state were similar in the two groups (Table 3).

Subgroup results

In patients with normal fasting triglyceride levels, mean triglyceride levels and percent changes of triglyceride levels in the postprandial state were similar at the fasting state, and 2nd, 4th, 6th and 8th hours after fat loading in both CAD group and the control group (Table 4). In the same subgroup of patients, the areas under the plasma triglyceride concentration curves were similar in CAD and control groups (Table 4). This subgroup of patients demonstrated a significant increase in triglyceride levels after fat loading (F=497.355; p<0.001), but this increase was similar in CAD and control groups (F=0.258; p=0.614).

Mean triglyceride levels in patients with elevated fasting triglyceride levels were higher in CAD group than control group at fasting state (p=0.072) but this difference was not significant (Table 4). After fat loading, triglyceride levels in patients with elevated fasting triglyceride levels were significantly higher in CAD group than control group at 2nd hours (p<0.001) and 4th hours (p=0.029) and were similar between two groups at 6th and 8th hours (Table 4). Percent changes of the triglyceride levels in the postprandial state in patients with elevated fasting triglyceride levels were higher in CAD group than control group at 2nd hours (p<0.010) and were similar between two groups at 4th, 6th and 8th hours (Table 4). In patients with elevated fasting triglyceride levels, the areas under the plasma triglyceride concentration curves were significantly higher in patients with CAD than control group (p=0.020) (Table 4). In general linear model analysis, patients with elevated triglyceride levels, the triglyceride levels were significantly increased in the follow up after fat loading compared to baseline triglyceride levels in CAD and control group (F=219.562; p<0.001) and those with CAD groups had significantly higher PPTG increase than controls (F=6.115; p=0.024).

Discussion

In this study, we found that, triglyceride levels were significantly increased after fat loading compared to baseline levels in CAD and control groups but these changes were not significantly different between the two groups. However, in the subgroup of patients with high fasting triglyceride levels, the triglyceride levels were significantly increased after fat loading in CAD group compared to the control group.

Hypertriglyceridemia has many varieties; however its relationship to atherosclerosis is well established. Adult Treatment Panel III recommends LDL cholesterol to be the primary target of therapy (6). After an adequate trial of dietary therapy for LDL lowering, attention should turn to atherogenic dyslipidemia and the metabolic syndrome. For atherogenic dyslipidemia, treatment strategy focuses on the triglyceride. Levels of fasting and PPTG are highly variable depending in part on the content of the last meal and on the duration from the last meal taken. Triglycerides are usually measured in the fasting state at the lowest triglyceride level of the day according to the guidelines (6) but recent studies suggest that nonfasting triglyceride levels may be superior to fasting triglyceride levels to predict CAD (9-16). Increased levels of nonfasting triglycerides may indicate the presence of increased levels of atherogenic remnant lipoproteins (7, 8, 23). Some experimental (24, 25) and clinical studies (8, 26, 27) have suggested that increased plasma lipoprotein

Table 4. Fasting and postprandial triglyceride levels for CAD patients and controls in patients with and without fasting triglyceride elevation

Variables	Patients without fasting triglyceride elevation			Patients with fasting triglyceride elevation		
	CAD group (n=29)	Control group (n=30)	p*	CAD group (n= 11)	Control group (n=10)	p*
Baseline TG levels, mg/dL	96±29 (96)	94±28 (97)	0.876	237±62 (227)	197±57 (170)	0.072
TG levels at 2nd hour, mg/dL	131±49 (120)	141±53 (144)	0.394	351±84 (362)	209±35 (208)	<0.001
Percent change at the 2nd hour, %**	+38 (25)	+50 (47)	0.173	+50 (49)	+10 (23)	0.010
TG levels at the 4th hour, mg/dL	143±54 (130)	150±60 (152)	0.560	388±129 (394)	261±78 (251)	0.029
Percent change at the 4th hour, %**	+51 (51)	+58 (57)	0.724	+63 (73)	+36 (39)	0.085
TG levels at the 6th hour, mg/dL	129±44 (139)	122±48 (122)	0.376	346±150 (294)	246±95 (210)	0.175
Percent change at the 6th hour, %**	+37 (30)	+27 (32)	0.372	+44 (43)	+26 (11)	0.331
TG levels at the 8th hour, mg/dL	98±31 (93)	98±36 (87)	0.711	265±94 (275)	200±85 (186)	0.175
Percent change at the 8th hour, %**	+7 (3)	+3 (0)	0.416	+11 (4)	+1 (-2)	0.201
Area under TG curve, mg/dL.h	121±37 (127)	128±45 (136)	0.614	334±103 (298)	233±58 (237)	0.020

Continuous variables are expressed as means±standard deviation (median)
*unpaired Student t- test and Mann-Whitney U test
CAD - coronary heart disease, TG - triglyceride
**Postprandial change in triglyceride levels compared to baseline triglyceride levels

remnant particles might contribute to atherosclerosis and postprandial hypertriglyceridemia, reflecting an elevated concentration of lipoprotein remnant particles, might therefore indicate increased risk for myocardial infarction, ischemic heart disease, and death.

Most of the data supporting the correlation of elevated PPTG levels and CAD come from cohort studies or subgroup analysis of large -scale trials (9-16). These studies were not randomized and the nonfasting state was not standardized. In these studies, investigators did not use any specific triglyceride loading protocols or a specific timing for measurement triglyceride levels (9-16). In most of these studies, different populations of patients were analyzed to evaluate the relation between fasting or nonfasting triglyceride levels and CAD (9-11, 13-16) as the same patients did not have fasting and nonfasting state triglyceride levels.

Case-control studies that evaluated the relationship between PPTG levels and CAD used different fat loading protocols in different patient groups and different results were found (17-21). The follow up period after fat loading is 4 to 24 hours in these trials. In some of these studies, a standard test meal similar to ours was used (17, 19, 20), in others vitamin A fat loading test was used (18, 21). In all the studies TG levels increased in patients with and without CAD after fat loading. In response to a meal, triglycerides and remnant lipoprotein concentrations both typically increase to their peaks by approximately between 3-5 hours (17-21) and triglyceride levels normally return to baseline fasting levels at 10 hours (28). In this study, the peak PPTG level was reached at the 4th hour and it decreased to almost basal values at the 8th hour.

In 2 case control studies, the fasting triglyceride levels were higher in patients with CAD but the difference was not significant which is similar to our results (19, 21).The difference between the PPTG levels at the 5th hour was significant in one of these studies (19), however in the other small scale study all PPTG levels were higher in the CAD group (21). In three case control studies, fasting triglyceride levels were significantly higher in patients with CAD and remained high in the follow up (17, 18, 20). Schaffer et al. (20) followed PPTG levels for 4 hour in their study. They found that fasting and PPTG levels at the 4th hour were significantly higher in CAD group, however, as in our results, the percent changes in triglyceride levels in the two groups after lipid loading were similar in both groups. In this study we observed that patients with CAD who had high fasting triglyceride levels had exaggerated responses to lipid loading resulting in a higher PPTG level, remaining high for a longer period of time. This finding is consistent with the results of previous trials (17-19).

Study limitations

The main limitation of this study is the plasma remnant protein levels which are important in the effect of PPTG in atherosclerosis were not measured. The sample size analysis was done for the hypothesis comparing the postprandial triglyceride levels in patients with and without coronary artery disease. We didn't find a significant difference between these groups. However, we discovered a significant difference in a subgroup that was not pre-specified, that is patients with high fasting triglyceride levels. Further studies with an appropriate sample size for this subgroup of patients are needed.

Conclusion

Our data show that high levels of PPTG may be important in patients with CAD who have a high fasting triglyceride level and high PPTG levels are not related to CAD in patients with normal fasting levels of triglyceride. We think that further, large-scale trials involving patients with high fasting triglyceride levels are needed to better clarify this finding.

Conflict of interest: None declared.

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