C-Reactive Protein, Homocysteine and Lipoprotein (a) Levels in Patients Who Have Myocardial Infarction With and Without Diabetes

Diyabeti Olan ve Olmayan Miyokard İnfarctüslü Hastalarda C-Reaktif Protein, Homosisteine ve Lipoprotein (a) Düzeyleri

**ABSTRACT**

Objective: Recently, determination and following of the high sensitivity C-reactive protein, homocysteine and lipoprotein (a) that are risk factors are promising at therapy for cardiovascular disease. We planned to investigate those probable cardiovascular risk factors in patients with myocardial infarction, with and without diabetes and control subjects. Material and Methods: We recruited 65 patients having myocardial infarction, 29 of them type 2 diabetic and 36 of them non-diabetic. We also included in our study 32 healthy controls. We compared all the findings of the groups including C-reactive protein, homocysteine and lipoprotein (a). Results: C-reactive protein and lipoprotein (a) levels of myocardial infarction patients with and without type 2 diabetes were statistically higher than control subjects, but their levels did not differ in patients with myocardial infarction with and without diabetes. Homocysteine levels were not different in all the groups. Conclusion: C-reactive protein and lipoprotein (a) but not homocysteine levels are associated with acute coronary events at least in Turkey. When a patient has myocardial infarction the levels of C-reactive protein and lipoprotein (a) may not be affected if the patient has diabetes.

**Key Words:** Myocardial infarction; diabetes mellitus, type 2; C-reactive protein; homocysteine; lipoprotein (a)

**ÖZET**

Amaç: Son zamanlarda yüksek derecede sensitif C-reactif protein, homosistein ve lipoprotein (a) gibi kardiyovasküler hastalığa ait risk faktörlerinin ölçülmesi ve takibi tedavide ümit vermektedir. Miyokardiyal enfarktusunun diabeti olan ve olmayan hastalarda ve kontrolde bu muhtemel risk faktörlerini araştırmaya karar verildi. **Gereç ve Yöntemler:** Yırtık dokusu tipi diyabetik, 36’sı diyabetik olmayan 65 myocard infarktus hastasını ve 32 sağlıklı kontrol kişisi çalışmaya aldı. C-reactif protein, homosistein ve lipoprotein (a) de dahil olmak üzere grupların tüm parametrelerini kıyasladı. **Bulgular:** Miyokardiyal enfarktus hastalarının C-reactif protein ve lipoprotein (a) seviyeleri istatistiksel olarak kontrollerden yüksek, fakat bu değerler diabeti olan ve olmayan enfarktus hastalar arasında farklılık göstermedi. Homosistein seviyeleri herhangi bir gruba değişik değildir. **Sonuç:** C-reactif protein ve lipoprotein (a) seviyelerinin, (homosistein seviyelerinin değil) en azından Türkiye’de akut koroner olaylar ile ilgili olduğunu düşünüyoruz. Bu çalışmadan miyokard infarktusun varsa C-reactif protein ve lipoprotein (a)’nin diyabet varlığında etkilenmediği karsılanyor.

Anhta Kelimeler: Miyokard infarktusu; diabetes mellitus, tip 2; C-reactif protein; homosistein; lipoprotein (a)

**Türkiye Klinikleri J Endocrin 2013;8(1):10-5**

The incidence and prevalence of diabetes mellitus (DM) are rapidly increasing worldwide, due almost exclusively to increases in type 2 diabetes mellitus (T2DM), as it represents more than 90% of all cases of diabetes.1 The excess risk of cardiovascular disease is two to eight fold higher in patients with diabetes compared to non-diabetic individuals of
similar age, sex and ethnicity. Furthermore among patients with coronary artery disease diabetes is associated with an increased risk of developing acute coronary syndrome and an increased risk of death after an acute myocardial infarction.

Despite the importance of blood lipids in coronary heart disease, 50% of all myocardial infarction (MI) occur among individuals without overt hyperlipidemia. Although the use of global prediction algorithms such as those derived from the Framingham Heart study greatly improves the detection of heart disease risk, as many as 20% of all coronary events occur in the absence of any of the classic major vascular risk factors. Thus, because of the considerable need to improve vascular risk detection, much research over the past decade has focused on the identification and evaluation of novel atherosclerotic risk factors. Although more than 100 emerging risk factors have been proposed for their potential to improve global risk assessment, high sensitivity C-reactive protein (hsCRP), homocysteine (Hcy) and lipoprotein (a) (Lp(a)) are promising ones. The role and importance of CRP, Hcy and Lp(a) in atherosclerosis and their cause-effect relationship have not still been determined.

Keeping in mind the complex relationship among cardiovascular disease, diabetes and cardiovascular risk factors, we planned to compare CRP, Hcy and Lp(a) levels in patients with myocardial infarction with and without type 2 diabetes mellitus.

### MATERIAL AND METHODS

#### PATIENTS

In this cross-sectional study 65 male patients aged from 45-90 years, having chest pain started in 6 hours consecutively admitted to the coronary unit of Ankara Training and Research Hospital, then diagnosed as acute myocardial infarction between November 2009 and February 2010 were included. Twenty nine of them were having and 36 of them were not having T2DM. Thirty two age matched healthy male control subjects were also recruited from the outpatient Clinic of Ankara Training and Research Hospital.

Subjects with female gender, patients with acute illness, malignancy, chronic diseases, hepatic or renal dysfunctions, conditions which may effect metabolic parameters (such as thyroid dysfunctions in history or nowadays), fever or infection, recently treated with antianemics or antibiotics, having diseases that may interfere serum hsCRP levels were excluded.

All the subjects gave written informed consent and this study was performed according to the principles of Declaration of Helsinki 2008. Ethical approval for the study was obtained from Ankara Training and Research Hospital Ethics Committee.

After detailed physical examination, in all subjects body weight and height were measured. Waist was measured when fasting, in standing position halfway between cortical edge and ili acid crest, whereas hip was measured at the greatest circumference around the buttocks, by a non elastic measure. Waist to hip ratio (WHR) were calculated. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). The diagnosis of myocardial infarction was based on the joint recommendations by the European Society of Cardiology and American College of Cardiology. Patients were receiving oral antidiabetics or insulin at least 1 year were accepted as having T2DM.

Blood was withdrawn for fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), insulin (FI), serum total and HDL cholesterol (HDL-C), triglyceride (TG), uric acid (UA), CRP, Hcy and Lp(a) levels in 12-24 hours of their admission. Another blood sample was taken for postprandial plasma glucose (PPPG) 2 hour after breakfast.

An indirect measure of insulin resistance was calculated from the fasting plasma insulin $(\mu$unit/ml) x fasting plasma glucose (mmol/l) /22.5 formula as homeostasis model assessment-insulin resistance (HOMA-IR).

Systolic and diastolic blood pressure (SBP and DBP) were measured after a 5 min rest in the sitting position with a sphygmomanometer. Blood pressure (BP) was determined at least three times at the right upper arm, and the mean was used in the
analysis. Korotkoff’s first phase was accepted as systolic and fifth phase as accepted as diastolic pressure.

LABORATORY METHODS
Plasma glucose, uric acid, total cholesterol, TG and HDL-C concentrations were determined by enzymo-molarimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanalyser. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL: Total cholesterol-HDL-TG/5). HbA1c was measured by turbidometric inhibition immunoassay in oto-analyser. FI was measured by TOSOH G7 HPLC system, hsCRP by immunoflowmetric tests with Beckman-Cutler device, Hcy with Agilend 1100 device by HPLC method and Lp(a) by nephelometric method.

METHODS
We compared all the parameters in control, myocardial infarction with DM (MI-DM), myocardial infarction without DM (MI-NonDM) groups.

STATISTICAL ANALYSIS
Calculations were performed using SPSS version 11.5 (Customer ID 30000105930). Student’s test was used to compare the groups. Data are presented as mean ± SD. A p value of < 0.05 was considered as statistically significant.

RESULTS
This study was performed with 32 healthy control males, 29 MI patients with DM and 36 MI patients without DM. All the demographic and laboratory findings of the groups were demonstrated in Table 1.

When we compared control subjects with patients MI-DM we found that SBP and DBP of the control group were statistically higher and FBG, PPBG, HbA1c, Lp(a) and hsCRP were statistically lower than MI-DM group. As controls and MI-NonMI were compared SBP and DBP of the control group were also statistically higher and hsCRP and Lp(a) were statistically lower than MI-NonDM group. In MI-DM and MI-NonDM groups only FBG, PPBG and HbA1c levels were high in MI-DM group, any other parameters were not different.

DISCUSSION
In our study we demonstrated that hsCRP and Lp(a) of the patients with MI either having DM or not, were higher than the controls, but these parameters did not differ in patients having MI with and without DM. Also we did not find any difference in Hcy levels in all groups.

Measurement of hsCRP, an inflammatory biomarker that independently predicts future vascu-
lar events improves global classification of risk, regardless of LDL-C levels.\textsuperscript{12,13} Studies have demonstrated that hsCRP is a strong predictor for risk of future MI even in patients without known macrovascular disease.\textsuperscript{14,15} CRP immunoreactive protein is also detected in the lesions of atherosclerosis, plasma CRP as well as lesional CRP was found to be associated with the formation and progression of atherosclerotic lesions.\textsuperscript{16} The serum levels of hsCRP was also demonstrated to be correlated with the risk\textsuperscript{17} and complications.\textsuperscript{18} The same correlation was also shown with cardiovascular disease morbidity and mortality in patients with T2DM.\textsuperscript{19} Finding higher hsCRP levels in our patients with MI either diabetic or non-diabetic than control subjects, we thought that we might find a difference when comparing hsCRP levels in diabetic and non-diabetic MI patients, but there were not a statistical difference. This result made us speculate that when the patients had an inflammation related serious condition such as myocardial infarction, being diabetic or not did not affect hsCRP levels.

Lp(a) is a low density lipoprotein like particle synthesized by the liver that consists of an apolipoprotein B100 molecule covalently linked to a very large glycoprotein known as apolipoprotein (a).\textsuperscript{20} It has been shown to enter the arterial intima of humans,\textsuperscript{21} in vitro and animal studies have reported that Lp(a) can promote thrombosis, inflammation and foam cell formation.\textsuperscript{22} Its use as an independent risk factor for cardiovascular disease still remains controversial, but prospective studies have reported positive associations of Lp(a) concentration with coronary artery disease risk.\textsuperscript{23,24} It has been also suggested that Lp(a) is associated with coronary heart disease only at very high concentrations.\textsuperscript{25,26} The association of Lp(a) and cardiovascular disease was also shown in type 2\textsuperscript{27} and type 1 diabetic patients.\textsuperscript{28} In our study we found high levels of Lp(a) in all our subjects including the controls. As in the study of Rohde et al. where hsCRP and Lp(a) levels were found to correlated,\textsuperscript{29} when we compared our patients with MI, either diabetic or not, Lp(a) were significantly high like hsCRP, but as in hsCRP, Lp(a) did not differ among MI patients with diabetes and without diabetes. This result also strenghtened our speculation that if the patients had an acute coronary event, whether they were diabetic or not Lp(a) levels, with hsCRP were not affected.

Hcy is a sulphur containing amino acid that is an intermediatery product in methionine metabolism. After Hcy mediated vascular disease was first established in the 1960’s, Hcy level was considered to be a marker of endothelial dysfunction and shown to be a predictor of cardiovascular disease in epidemiological studies,\textsuperscript{30,31} but uncertainties in this area have still existed. In diabetic patients, homocyssteine levels were significantly increased compared with healthy subjects an hyperhomocysteinaemia was assumed as an independent risk factor for macro-microangiopathy and mortality.\textsuperscript{32,33} Keeping in mind its probable role in cardiovascular abnormalities we wanted to evaluate Hcy levels in our diabetic and non diabetic patients with MI, but we failed to find any difference in our MI groups and control subjects. This result might have made us conclude that Hcy did not have an important role in acute coronary events in at least our population. However Hcy levels of all the males both patient and control were high, as patients having Hcy levels higher than 16 μmol/ml were prone to coronary events, we recommend that the males like our patients must be followed with much attention.

We found that our MI patients, both diabetic and non-diabetic had lower systolic and diastolic blood pressure levels compared to control subjects. We may explain this result; we included the MI patients when they were taken to coronary unit and treatment for coronary event was started, such as beta blocker or angiotensin converting enzyme inhibitors. Patients with DM and cardiovascular disease may also had had prescribed antihypertensives before they admitted to the hospital. Total cholesterol, LDL-C, HDL-C and TG levels of all the groups were not statistically different. We may explain this with their possible previous lipid lowering medications.

All our males, among control and patient groups had indifferent body mass indices, and we
did not find any statistical difference in their waist circumference and waist hip ratios. It was interesting that all the patients with MI or DM and all the control persons were obese. We could not be able to explain this result, but we may say that our people are getting fatter.

Some methodological issues have to be addressed. We did not consider if our patients were being treated with statins. In this regard these drugs have been reported to decrease the levels of CRP. Therefore, it may be said that these medications might have affected beneficially our results, although CRP levels of MI groups were high. Also as to antidiabetic medications, a considerable number of our patients were being treated with glitazones, insulin sensitizing drugs reported to reduce CRP. Second, our study was a cross-sectional one, performed in a single center, so it lacks of generalizability to Turkish population. Additionally, enlargement of sizes of the groups are needed.

Despite the aforementioned limitations of our study, in conclusion, hsCRP and Lp(a) levels were high in patients with myocardial infarction, but if such a serious cardiovascular event existed diabetes did not change those levels. We also speculate that Hcy levels did not have a role in cardiovascular disease in at least our Turkish population.

REFERENCES


