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

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

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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-reaktif protein, homosistein ve lipoprotein (a) gibi kardiyovasküler hastalığa ait risk faktörlerinin ölçülmesi ve takibi tedavide ümit vermektedir. Miyokardiyal infartktüslü diabeti olan ve olmayan hastalarda ve kontrollerde bu muhtemel risk faktörlerini araştırmayı planladık. **Gereç ve Yöntemler:** Yirmi dokuzu tip 2 diyabetik, 36'sı diyabetik olmayan 65 myokard infarktüs hastasını ve 32 sağlıklı kontrol kişiyi çalışmaya aldık. C-reaktif protein, homosistein ve lipoprotein (a) de dahil olmak üzere grupların tüm parametrelerini kıyasladık. **Bulgular:** Diyabeti olan ve olmayan miyokardiyal infarktüs hastalarının C-reaktif protein ve lipoprotein (a) seviyeleri istatistiksel olarak kontrollerden yüksekti, fakat bu değerler diyabeti olan ve olmayan infarktüslü hastalar arasında farklılık göstermedi. Homosistein seviyeleri hiçbir grupta değişik değildi. **Sonuç:** C- reaktif protein ve lipoprotein (a) seviyelerinin, (homosistein seviyelerinin değil) en azından Türkiye'de akut koroner olaylar ile ilgili olduğunu düşünüyoruz. Bir hastada miyokard infarktüsü varsa C- reaktif protein ve lipoprotein (a)'nın diyabet varlığından etkilenmediği kanısındayız.

Anahtar Kelimeler: Miyokard infarktüsü; diabetes mellitus, tip 2; C-reaktif protein; homosistein; lipoprotein (a)

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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.[2,3] 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.[4,5]

Despite the importance of blood lipids in coronary heart diesease, 50% of all myocardial infarction (MI) occur among individuals without overt hyperlipidemia.[6] Although the use of global prediction algorithms such as those derived from the Framingham Heart study greatly improves the detection of heart disease risk,[7] as many as 20% of all coronary events occur in the absence of any of the classic major vascular risk factors.[8] 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.[9] 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.[10] The role and importance of CRP, Hcy and Lp(a) in atherosclerosis and their cause-effect relationship have not stil 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 Decleration of Helsinki 2008. Ethical approval for the study was obtained from Ankara Training and Research Hospital Ethics Committe.

After detailed physical examination, in all subjects body weight and height were measured. Waist was measured when fasting, in standing position halfway between costal edge and iliac 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.[11] 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 (μunite /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 semi-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 was accepted as diastolic pressure.

LABORATORY METHODS

Plasma glucose, uric acid, total cholesterol, TG and HDL-C concentrations were determined by enzymocalorimetric 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 otoanalyser. 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.

TABLE 1: Demographic and laboratory findings of the groups.

	Control n:32 Group1	MI-DM n:29 Group2	MI-NonDM n:36 Group3
Age(year)	57.4±6.3	63.9±11.7	59.6±13.3
BMI(kg/m2)	30.3±4.0	30.4±4.8	30.0±4.0
Waistcir.(cm)	103.9±10.8	96.1±16.7	99.5±13.2
WHR	1.7±0.4	1.5±0.5	1.7±0.4
SBP(mmHg)	132.1±19.0a	112.4±16.2	117.3±24.9b
DBP(mmHg)	82.0±11.3a	69.0±11.3	74.5±13.3b
FBG(mg/dl)	90.5±9.4a	145.6±52.6c	86.9±9.2
PPBG(mg/dl)	115.4±33.4a	237.6±93.4c	120.5±30.1
HbA1c(%)	5.4±0.4a	7.4±1.5c	5.4±0.6
FI(µU/ml)	16.2±4.0	13.6±10.9	15.2±9.7
HOMA-IR	3.2±2.8	4.7±3.3	3.5±2.6
T.Chol.(mg/dl)	187.0±41.3	173.3±45.1	191.7±50.7
LDL-C(mg/dl)	115.7±34.2	107.8±43.5	118.5±48.3
HDL-C(mg/dl)	39.7±6.0	36.2±8.1	36.0±10.8
TG(mg/dl)	171.2±94.2	176.8±90.6	158.7±78.2
CRP(mg/dl)	3.5±2.3a	47.6±7.1	51.7±9.5b
Hcy(µmol/ml)	15.8±9.8	15.7±5.6	19.0±9.5
UA(mg/dl)	5.6±1.1	6.5±2.2	5.7±1.4
Lp(a)(mg/dl)	229.0±49.7a	477.5±294.1	496.5±388.8b

MI-DM: Patients with myocardial infarction and diabetes mellitus, MI-NonDM: Patients with myocardial infarction and without diabetes mellitus, BMI: Body mass index, Waist cir.: Waist circumference, WHR: Waist hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, PPBG: Post prandial blood glucose HbA1c: Hemoglobin A1c, FI: Fasting insulin, HOMA-IR: Homeostasis model assesment index-insulin resistance, T.Chol: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride, CRP: C-reactive protein, Hcy: Homocysteine, Lp(a): Lipoprotein (a). Data are presented as mean ± SD. NS: Nonsignificant.
a:Difference between Group I and II is statistically significant ($p < 0.05$)
b:Difference between Group I and III is statistically significant ($p < 0.05$)
c:Difference between Group II and III is statistically significant ($p < 0.05$)

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.[12,13] Studies have demonstrated that hsCRP is a strong predictor for risk of future MI even in patients without known macrovascular disease.[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 atherosclerostic lesions.[16] The serum levels of hsCRP was also demonstrated to be correlated with the risk[17] and complications.[18] The same correlation was also shown with cardiovascular disease morbidity and mortality in patients with T2DM.[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).[20] It has been shown to enter the arterial intima of humans,[21] in vitro and animal studies have reported that Lp(a) can promote thrombosis, inflammation and foam cell formation.[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.[23,24] It has been also suggested that Lp(a) is associated with coronary heart disease only at very high concentrations.[25,26] The association of Lp(a) and cardiovascular disease was also shown in type 2[27] and type 1 diabetic patients.[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,[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,[30,31] but incertainties in this area have still existed. In diabetic patients, homocysteine levels were significantly increased compared with healthy subjects an hyperhomocysteinaemia was assumed as an independent risk factor for macro-microangiopathy and mortality.[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. Additionaly, 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

1. Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, et al. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. Diabetes Care 2001;24(11): 1936-40.
2. Grundy SM, Howard B, Smith S Jr, Eckel R, Redberg R, Bonow RO. Prevention Conference VI: Diabetes and Cardiovascular Disease: executive summary: conference proceeding for healthcare professionals from a special writing group of the American Heart Association. Circulation 2002;105(18):2231-9.
3. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB. Mortality among diabetics in a national sample. Am J Epidemiol 1988;128(2):389-401.
4. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. JAMA 1999;281(14):1291-7.
5. Öztürk A, Gürsoy G, Acar Y, Demirbaş B, Eşbah O, Kırnap NG, et al. Glucose Metabolism in Patients with Acute Coronary Syndrome Without Having History of Diabetes Mellitus. Turkiye Klinikleri J Cardiovasc Sci 2011;23(3):170-6.
6. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996;144(6):537-47.
7. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286(2):180-7.
8. Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol 2004;29(8):439-93.
9. Brotman DJ, Walker E, Lauer MS, O'Brien RG. In search of fewer independent risk factors. Arch Intern Med 2005;165(2):138-45.
10. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107(3):499-511.
11. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36(3):959-69.
12. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351(25):2599-610.
13. Boekholdt SM, Hack CE, Sandhu MS, Luben R, Bingham SA, Wareham NJ, et al. C-reactive protein levels and coronary artery disease incidence and mortality in apparently healthy men and women: the EPIC-Norfolk prospective population study 1993-2003. Atherosclerosis 2006;187(2):415-22.
14. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. Circulation 2004;109(16):1955-9.
15. Sellmayer A, Limmert T, Hoffmann U. High sensitivity C-reactive protein in cardiovascular risk assessment. CRP mania or useful screening? Int Angiol 2003;22(1):15-23.
16. Yu Q, Li Y, Wang Y, Zhao S, Yang P, Chen Y, et al. C-reactive protein levels are associated with the progression of atherosclerotic lesions in rabbits. Histol Histopathol 2012; 27(4):529-35.
17. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, et al. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes 2002;51(5):1596-600.
18. Kang ES, Kim HJ, Ahn CW, Park CW, Cha BS, Lim SK, et al. Relationship of serum high sensitivity C-reactive protein to metabolic syndrome and microvascular complications in type 2 diabetes. Diabetes Res Clin Pract 2005;69(2):151-9.
19. Kengne AP, Batty GD, Hamer M, Stamatakis E, Czernichow S. Association of C-reactive protein with cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants from four U.K. prospective cohort studies. Diabetes Care 2012;35(2):396-403.
20. Anuurad E, Boffa MB, Koschinsky ML, Berglund L. Lipoprotein(a): a unique risk factor for cardiovascular disease. Clin Lab Med 2006;26(4):751-72.
21. Nielsen LB, Grønholdt ML, Schroeder TV, Stender S, Nordestgaard BG. In vivo transfer of lipoprotein(a) into human atherosclerotic carotid arterial intima. Arterioscler Thromb Vasc Biol 1997;17(5):905-11.

22. Boffa MB, Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for atherosclerosis and thrombosis: mechanistic insights from animal models. Clin Biochem 2004; 37(5):333-43.

23. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. Circulation 2000;102(10): 1082-5.

24. Bennet A, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. Arch Intern Med 2008;168(6):598-608.

25. Suk Danik J, Rifai N, Buring JE, Ridker PM. Lipoprotein(a), measured with an assay independent of apolipoprotein(a) isoform size, and risk of future cardiovascular events among initially healthy women. JAMA 2006;296(11): 1363-70.

26. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation 2008;117(2):176-84.

27. Albahrani A, Alkindi M, Marks E, Alyahyaee S, Shenkin A. Lipoprotein(a): an independent risk factor for ischemic heart disease that is dependent on triglycerides in subjects with type 2 diabetes mellitus. Lipids Health Dis 2007;6:26.

28. Kollerits B, Auinger M, Reisig V, Kästenbauer T, Lingenhel A, Irsigler K, et al. Lipoprotein(a) as a predictor of cardiovascular disease in a prospectively followed cohort of patients with type 1 diabetes. Diabetes Care 2006;29(7): 1661-3.

29. Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. Am J Cardiol 1999;84(9):1018-22.

30. Sabanayagam C, Shankar A. Association between plasma homocysteine and microalbuminuria in persons without hypertension, diabetes mellitus, and cardiovascular disease. Clin Exp Nephrol 2011;15(1):92-9.

31. Lietava J, B BV, Dukat A, Fodor GJ. Homocysteine Slovakia study: study design and occurrence of hyperhomocysteinaemia and other risk factors. Bratisl Lek Listy 2012; 113(2):80-6.

32. Noll C, Lacraz G, Ehses J, Coulaud J, Bailbe D, Paul JL, et al. Early reduction of circulating homocysteine levels in Goto-Kakizaki rat, a spontaneous nonobese model of type 2 diabetes. Biochim Biophys Acta 2011;1812(6): 699-702.

33. Wotherspoon F, Laight DW, Browne DL, Turner C, Meeking DR, Allard SE, et al. Plasma homocysteine, oxidative stress and endothelial function in patients with Type 1 diabetes mellitus and microalbuminuria. Diabet Med 2006;23(12):1350-6.