Increased lipoprotein(a) in metabolic syndrome: Is it a contributing factor to premature atherosclerosis?

Metabolik sendromu bulunan hastalarda artmış lipoprotein (a) düzeyi: Erken ateroskleroz gelişimi için bir risk faktörü olabilir mi?

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ABSTRACT

Objective: It is well known that patients with metabolic syndrome (MS) have a greater risk of developing coronary artery disease (CAD). However, the association of novel coronary risk factors with MS has not been well established. In this study, we sought to investigate the association of lipoprotein (a) [Lp(a)], homocysteine (Hcy), uric acid, and C-reactive protein (CRP) levels with MS.

Methods: We enrolled 355 consecutive patients from our outpatient cardiology clinic into this cross-sectional, controlled study-186 with MS and 169 without MS, according to the Adult Treatment Panel III criteria. Serum Hcy, Lp(a), uric acid, and CRP levels were determined and compared between the groups.

Results: The groups were homogenous with regard to age, sex, and other demographic variables (all p>0.05). As expected, the prevalence of hypertension (85.4% vs 55.6%, p<0.001) and dyslipidemia (78.3% vs 62.6%, p<0.05) were higher in patients in the MS group. Patients were compara ble with respect to smoking (28.4% vs 24.8%, p =0.4) and family history of CAD (46.1% vs 40.8%, p=0.3). Patients with MS had significantly higher Lp(a) levels [29.2 (13.4-45.7) vs 16.2 (9.5-26.2) mg/dL; p<0.0001] compared with controls, whereas Hcy (12.2±4.8 vs 12.3±4.9 µmol/L; P=0.8), uric acid (5.7±1.6 vs 5.3±1.3 mg/dL; p=0.08), and CRP levels [6.0 (3.7-9.3) vs 5.1 (3.2-7.6) mg/L; p=0.07] were similar.

Conclusion: Patients with MS seems to have increased serum levels of Lp(a), which might contribute to the premature atherosclerosis observed in these patients. Further research is needed to better clarify this issue. *(Anadolu Kardiyol Derg 2008; 8: 111-5)*

Key words: Metabolic syndrome, lipoprotein(a), homocysteine, uric acid

ÖZET

Amaç: Metabolik sendromu (MS) bulunan hastalar artmış koroner arter hastalığı (KAH) riskine sahiptirler. Yeni tanımlanan koroner risk faktörleri ile MS arasındaki ilişki net olarak bilinmemektedir. Bu çalışmada MS olan ve olmayan hastalarda lipoprotein (a) [Lp(a)], homosistein (Hcy), ürik asid ve C-reaktif protein (CRP) düzeylerinin ölçülmesi amaçlandı.

Yöntemler: Kesitsel, kontrollü olarak planlanan çalışmaya hastanemiz kardiyoloji kliniğine ayaktan başvuran 355 hasta (186 MS, 169 kontrol) dahil edildi. MS ATP III kriterlerine göre tanımlandı. Serum Lp(a), Hcy, ürik asid ve CRP düzeyleri ölçülerek gruplar arasında karşılaştırıldı.

Bulgular: Gruplar yaş, cinsiyet ve diğer demografik özellikler açısından benzer idi (p >0.05). Bekleneceği üzere hipertansiyon (%85.4 ve %55.6, p<0.001) ve dislipidemi (%78.3 ve %62.6, p<0.05) prevalansı MS olan hastalarda anlamlı şekilde daha fazla idi. Sigara kullanımı (%28.4 ve %24.8, p=0.4) ve ailede KAH öyküsü (%46.1 vs %40.8, p=0.3) ise farklı değildi. Serum Lp(a) düzeyi MS olan hastalarda kontrol grubuna oranla anlamlı şekilde daha yüksek saptandı [29.2 (13.4-45.7) ve 16.2 (9.5-26.2) mg/dL; p<0.0001], ancak Hcy (12.2±4.8 ve 12.3±4.9 µmol/L; p=0.8), ürik asid (5.7±1.6 ve 5.3±1.3 mg/dL; p=0.08) ve CRP [6.0 (3.7-9.3) vs 5.1 (3.2-7.6) mg/L; p=0.07] düzeyleri gruplar arasında benzer bulundu.

Sonuç: Bu bulgular MS bulunan hastalarda serum Lp(a) düzeyinin yüksek olabileceğini ve bu hastalarda izlenen erken aterosklerozdan sorumlu olabileceğini düşündürmektedir. Bu konunun daha iyi aydınlatılabilmesi için ileri çalışmalara ihtiyaç vardır. *(Anadolu Kardiyol Derg 2008; 8: 111-5)*

Anahtar kelimeler: Metabolik sendrom, lipoprotein(a), homosistein, ürik asit

Introduction

Patients with metabolic syndrome (MS) have an aggregation of atherosclerotic risk factors (1). It is well known that patients with this syndrome have a greater risk of developing coronary artery disease (CAD) (1, 2).

As the burden of CAD on the population has become well understood, some so-called novel atherosclerotic risk factors have gained particular attention in recent years (3-5). The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) has identified low-density lipoprotein (LDL)

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cholesterol as the primary target of risk reduction therapy, followed by MS as the secondary target (1). This is because of that each component of this syndrome is by itself a risk factor for atherosclerotic vascular disease. When the importance of novel coronary risk factors and MS were considered, it becomes possible to believe that a correlation between these risk factors and MS might exist.

Risk reduction and good metabolic control effectively decrease the development of atherosclerotic vascular disease. Therefore, primary prevention in this regard is very important in patients who seem otherwise healthy but have MS, since they harbor many coronary risk factors. Therefore, identifying an association between novel coronary risk factors and MS is quite important; with it, preventive measures may be applied to avoid the potential harm of each of these risk factors. However, the association between novel coronary risk factors and MS is not well established.

In this study, we aimed to investigate the association of some novel coronary risk factors, as serum levels of lipoprotein (a) [Lp(a)], homocysteine (Hcy), uric acid, and C-reactive protein (CRP) with MS.

Methods

The study was designed as a cross-sectional, controlled study. After the research protocol was approved by the local ethics committee and informed consent was obtained from each subject we enrolled 355 consecutive patients in our cardiology outpatient clinic into this study-186 with MS and 169 without MS as the control group, according to ATP III criteria (1). Of the patients with MS 159 had hypertension and 37 had CAD; while in the control group there were 93 patients with hypertension and 17 with CAD. Patients having 3 or more of the following criteria were considered as having MS:

1. Fasting blood glucose level greater than 110 mg/dL
2. Serum triglyceride level greater than 150 mg/dL
3. Serum high-density lipoprotein (HDL) cholesterol level less than 40 mg/dL in men, and less than 50 mg/dL in women
4. Blood pressure of 130/85 mm Hg or more
5. Waist circumference greater than 102 cm in men, and greater than 88 cm in women

Detailed medical history was obtained. Patients having acute infectious/inflammatory conditions, acute coronary syndromes, renal dysfunction, gout disease, or familial hyperlipidemia were excluded from the study. Dyslipidemia was defined as a total cholesterol level greater than 200 mg/dL, LDL cholesterol level greater than 130 mg/dL, HDL cholesterol level less than 40 mg/dL, or a triglyceride level greater than 150 mg/dL. Angiographically proven CAD was defined as the presence of at least 50% narrowing in 1 or more of the coronary arteries.

Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest. Blood samples were taken after 12 hours of overnight fasting. Serum Lp(a), Hcy, uric acid, and CRP levels were determined and compared between the groups. Levels of Lp(a) were determined by the immunoturbidimetric method using a PP modular autoanalyser (Roche Diagnostics, GmbH, Mannheim, Germany). Plasma Hcy levels were obtained using fluorescent polarizing enzyme immunoassay (Axis Biochemical ASA, Oslo, Norway). C-reactive protein levels were measured by the immunoturbidimetric method (Roche Diagnostics, GmbH, Mannheim, Germany). Using this method, the reference limit is less than 6 mg/L. Patients were divided into tertiles according to CRP levels. The lowest level comprised patients having CRP levels lower than 3 mg/L; the middle tertile comprised patients having CRP levels between 3 and 6 mg/L, and those with CRP levels that were greater than 6 mg/L made up the highest tertile. Serum uric acid level was measured by the enzymatic calorimetric method using a PP modular autoanalyser (Roche Diagnostics).

Statistical analyses

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 9.0, SPSS Inc, Chicago, Ill, USA). The sample size of the study was calculated according to the results of previous studies (6, 7) with significance of level 5% and power of the study of 80%. Continuous variables were compared using the Student t test, and qualitative variables were compared using the Chi-square test. For comparison of continuous variables that were not homogenously distributed, the nonparametric Mann-Whitney U test was used. Continuous variables were expressed as means ± standard deviation. Values for p less than 0.05 were considered as statistically significant.

Results

The mean age of patients in the study population was 60.0±10.0 years, and 246 (69.3%) were female. Patients with and without MS were homogenous with regard to age, sex, and other demographic variables (all $p>0.05$) (Table 1). As expected, prevalence of hypertension, dyslipidemia and diabetes mellitus (all $p<0.05$) were higher in patients in the MS group, whereas patients in both groups were comparable with respect to smoking and family history of CAD (all $p>0.05$) (Table 1). Mean value of body mass index was significantly higher in the MS group than it was in control subjects (30.3±4.5 vs 27.6±4.6kg/m^2; $p<0.001$). The medications that the patients were receiving are presented in table 1. The ratio of use of statins, angiotensin converting enzyme inhibitors or angiotensin receptor blockers and diuretics were higher in the MS group while the use of beta blockers and calcium channel blockers were similar between both groups.

Patients with MS had significantly higher Lp(a) levels compared with controls, whereas Hcy, uric acid and CRP levels were similar between the groups (Table 2). The distribution of Lp(a) levels in the study and control groups is presented in Figure 1. The ratio of patients having high Lp(a) (≥30mg/dL) was significantly higher in participants with MS than those without (Table 2). Compared with those in the control group, more patients with MS had CRP levels in the highest tertile; however, this difference was not statistically significant (49.7% vs 38.5%; $p=0.1$). The ratios of patients in the lowest (16.2% vs 22.4%; $p=0.1$) and intermediate (34.1% vs 39.1%; $p=0.1$) tertiles were also similar between groups.

History of myocardial infarction, coronary revascularization procedures, coronary artery bypass grafting surgery, and percutaneous coronary interventions were higher in patients having MS than those without this syndrome (p<0.05). Despite similar incidence of coronary angiographic examinations in both groups, the prevalence of CAD was significantly higher in patients in the MS group (p<0.05).

Table 1. Patient characteristics and laboratory findings

Variables	MS (n=186)	No MS (n=169)	p
History			
Sex, F/M	128/58	118/51	ns
Age, years	59.9±9.5	60.1±10.5	ns
History of MI, %	13.5	7.1	<0.05
CABG, %	1.8	5.3	<0.05
PCI, %	10.7	4.7	<0.05
CAD, %	20.0	10.3	<0.05
Hypertension, %	85.4	55.6	<0.0001
Dyslipidemia, %	78.3	62.6	<0.05
Diabetes mellitus, %	36.6	8.0	<0.05
Smoking, %	28.4	24.8	ns
Family history of CAD, %	46.1	40.8	ns
Medications			
ACEI/ARB, %	46.2	23.1	<0.0001
Beta blocker, %	25.3	20.1	ns
Diuretic, %	31.7	18.9	<0.05
CCB, %	22.6	16.0	ns
Statin, %	33.3	14.8	<0.05
Echocardiography			
LVH, %	74.7	61.7	<0.05
Wall motion abnormality, %	22.8	17.0	ns
Laboratory variables			
Glucose, mg/dL	107±21	95±13	<0.0001
Total cholesterol, mg/dL	211±39	205±48	ns
HDL cholesterol, mg/dL	45.2±10.5	56.7±13.6	<0.0001
LDL cholesterol, mg/dL	131±33	121±31	ns
Triglycerides, mg/dL	206±92	141±119	<0.0001

Data are represented as Mean±SD or percentages/proportions

Chi-square or Students` unpaired t tests

ACEI- angiotensin converting enzyme inhibitor, ARB- angiotensin receptor blocker, CABG- coronary artery bypass grafting, CAD- coronary artery disease, LVH- left ventricular hypertrophy, MI- myocardial infarction, MS- metabolic syndrome, ns- non significant, PCI- percutaneous coronary intervention

Discussion

The present study demonstrates that in addition to well-defined conventional atherosclerotic risk factors, patients with MS seems to have higher levels of Lp(a) than those without MS. However, levels of Hcy, uric acid, and CRP seem to be similar.

When we look at the components of the MS, we see that each of them is an independent risk factor for development of CAD. Regardless of the level of LDL cholesterol and other risk factors, MS confers an increased risk for CAD development (2). The ATP III recognizes that CAD risk is influenced by two groups of risk factors: the first includes those that are related to life habits including obesity, physical inactivity, and atherogenic diet. The second group includes high levels of Lp(a) and Hcy, prothrombotic, and proinflammatory state, and impaired glucose tolerance (1). As we can see, some of these risk factors are modifiable with simple precautions, while others are not.

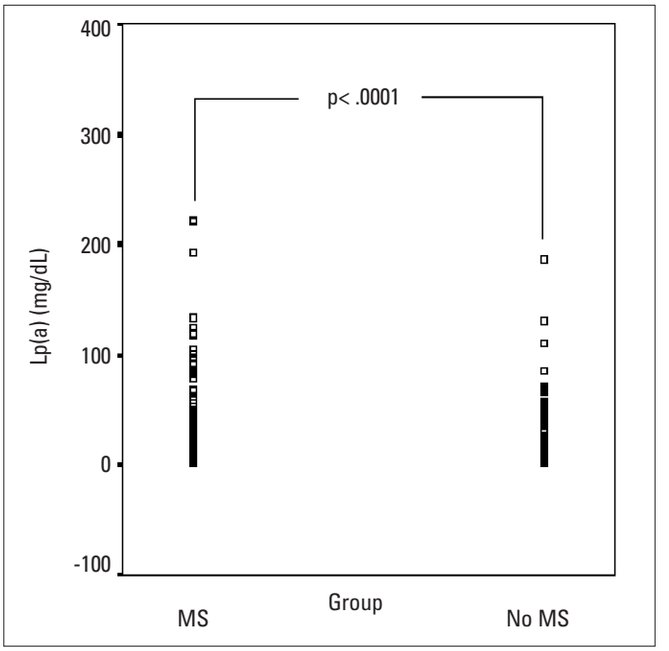

Figure 1. Distribution of Lp(a) values in patients with (A) and without (B) metabolic syndrome

Lp(a)- lipoprotein (a), MS- metabolic syndrome

Table 2. Comparison of the novel atherosclerotic risk factors in patients with and without metabolic syndrome

Variables	MS (n=186)	No MS (n=169)	p
Lp(a), mg/dL	29.2 (13.4-45.7)	16.2 (9.5-26.2)	<0.0001[a]
Lp(a) log	1.39±0.40	1.22±0.34	<0.0001
High Lp(a) (>30mg/dL), %	51.4	21.6	<0.0001[c]
Homocysteine, µmol/L	12.2±4.8	12.3±4.9	0.8[b]
Uric acid, mg/dL	5.7±1.6	5.3±1.3	0.08[b]
C-reactive protein, mg/L	6.0 (3.7-9.3)	5.1 (3.2-7.6)	0.07[a]

Data are represented as Mean±SD, Median (Minimum-Maximum) or percentages/proportions
[a]Mann-Whitney U test, , [b]Students` unpaired t-test, [c]Chi-square test
Lp(a) - Lipoprotein (a), log - logarithmic transformation, MS - metabolic syndrome

It has been shown that plasma Lp(a) level is an independent risk factor for CAD development (3). A study involving 9133 men aged 50 to 59 years without manifest cardiovascular disease revealed that Lp(a) is significantly related to CAD development and appeared to be a significant risk factor (4). Additionally, this study showed that patients with Lp(a) levels in the highest quartile had more than 1.5 times the risk than did patients whose Lp(a) levels were in the lowest quartile.

To our knowledge, data regarding Lp(a) levels in patients with MS are very limited and contrasting. There are some studies evaluating the association between Lp(a) and obesity. A study involving women with polycystic ovary syndrome revealed that levels of Lp(a) was higher in obese patients than those in the non-obese subjects (6). Two other reports established a relationship between Lp(a) level and obesity (7, 8). However, another study from Japan showed opposite results, that is, Lp(a) levels were lower in obese than in non-obese patients (9). De Pergola et al. (10) reported that levels of Lp(a) was similar between obese and non-obese subjects. Several factors are proposed to play role in affecting Lp(a) levels in these studies. Genetic and environmental factors including dietary habits are among those factors. Renal failure, inflammatory conditions, growth hormone therapy are among the non-genetic causes of increased Lp(a) levels. Lack of standardization of the technique for Lp(a) quantification, medications used are among the other factors affecting Lp(a) levels.

In the present study, we found that patients having MS had significantly higher Lp(a) levels than did patients without this syndrome. Of note, mean levels of Lp(a) was above ≥30mg/dL in patients with MS that is a level above which previous studies suggested an increase in the risk of premature atherosclerosis (11). Also, the percentage of patients having high Lp(a) was significantly higher in participants with MS than those without (Table 2). This might be responsible for the increased prevalence of premature atherosclerosis in patients having MS. Here we should point out that, unlike above findings from different studies, besides obesity other components of MS which are by themselves are independent risk factors for atherosclerosis may contribute to higher Lp(a) levels in this study.

Lipoprotein(a) is formed by the linkage of an LDL particle with apolipoprotein(a) and accepted as kind of a modified form of LDL. It is thought to play role in the development of atherosclerosis by inhibiting fibrinolysis, and also binds to macrophages and promotes foam cell formation. Considering the importance of Lp(a) as an atherosclerotic risk factor and our findings in the present study we hypothesized that it might have a role in the premature vascular involvement in these patients.

Hyperhomocysteinemia is another risk factor for atherosclerosis. High Hcy concentrations are thought to cause endothelial damage, inducing atherosclerosis (12). The relationship between elevated serum Hcy levels and CAD has been established (5). However, the relationship between hyperhomocysteinemia and MS, if it exists at all, has not been well studied.

In some studies it has been reported that there is a relation between hyperhomocysteinemia and MS or the components of this syndrome (13, 14). However some authors have reported no such a relation between Hcy levels and the components of MS (15, 16). As we can see, although results are conflicting, more data demonstrate no relationship between Hcy levels and insulin resistance in nondiabetic patients (15-17). In our study, in line with previous reports, we did not observe any difference in Hcy levels between patients with or without MS.

It is well known that inflammation plays a crucial role in both the initiation and progression of atherosclerosis. Data indicate that inflammation is associated with insulin resistance and MS (18, 19). The exact source of inflammation in patients with MS is not exactly known. Several mechanisms have been proposed to play role in this inflammatory process. One such mechanism is that some components of MS, like hypertension and dyslipidemia, may directly cause endothelial dysfunction, which leads to inflammation. Another explanation is that insulin resistance may increase hepatic CRP synthesis through blockade of insulin-mediated inhibition of acute-phase protein gene expression (20).

A study conducted by Lee and coworkers (21) is noteworthy in that they demonstrated that CRP level elevates in parallel as the number of components of MS increases. That is, patients having only 1 component of the syndrome have lowest, while those with all 5 components have highest, CRP levels. In one study, CRP level was found to correlate with obesity but not with other components of the MS (22). Another study revealed that CRP concentration increases as the BMI or blood pressure increases and the HDL decreases (23).

The levels of serum CRP although had a trend towards being higher in MS group were similar between patients with and without MS in the present study. The lack of an association in our study might have resulted from the fact that we measured conventional CRP instead high sensitive CRP, which might have led to such an association.

Uric acid is another newly described coronary risk factor. Studies have shown that high uric acid levels are associated with increased cardiovascular disease and mortality (24-26). However, data regarding uric acid levels in MS are limited. Denzer and coworkers found that uric acid levels in obese young boys are associated with total cholesterol/HDL ratio, triglycerides, BMI, and systolic blood pressure (27). The authors concluded that uric acid might be an indicator of pre-MS in obese youths.

Bonora and colleagues (28) determined serum uric acid levels in 957 young men. They found that uric acid levels were correlated with MS. A study from Italy revealed similar results. Serum uric acid levels have been found to be associated with BMI, waist/hip ratio, fasting insulin, serum triglycerides, LDL, and diastolic blood pressure in healthy men and women (29). In contrast to these studies, in the present study, we found similar levels of uric acid in patients in our outpatient population both with and without MS.

Despite a similar frequency of coronary angiographic examinations in both groups, CAD was more prevalent in patients having MS. In addition, there was a greater history of myocardial infarction, coronary artery bypass grafting surgery, and percutaneous coronary intervention in patients with MS.

Limitations

There are several limitations of this study. First, some patients in the control group had 1 or 2 components of the MS. When we compare the two groups, they may have common clinical

characteristics and laboratory results. Second, high sensitive CRP, instead of conventional CRP, would have led to more valuable information as a sign of inflammation caused by atherosclerosis. Finally, we did not measure insulin resistance directly. If we had done so, that might have led to more reliable results.

Conclusion

Patients with MS have significantly increased serum levels of Lp(a), which might contribute to the premature atherosclerosis seen in these patients. To better define the therapeutic approach and to take necessary precautions to prevent cardiovascular disease, we believe that detailed evaluation that includes determining the novel coronary risk factors should be done for risk stratification of patients having MS. Further studies with larger number of patients are needed to better clarify this issue.

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