Is Serum Lipoprotein (A) Level Elevated in Preeclampsia Patients?

Preeklampsi Tanılı Hastalarda Serum Lipoprotein (A) Seviyesi Yüksek midir?

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ABSTRACT

Aim: To examine the serum Lipoprotein (Lp) (a) levels in preeclamptic cases and its relation with the severity of preeclampsia.
Materials and Methods: Forty cases over 28 gestational weeks were included in this study, out of which 10 had mild preeclampsia (group 1), 10 had severe preeclampsia (group 2) and 20 were women with normal pregnancy (group 3). Platelet count, levels of total protein, albumin, fibrinogen, serum Lp (a) and prothrombin time were compared between the groups.
Results: Significant differences were found between the groups as regards total protein, albumin and platelet values (p<0.001, p<0.001, and p:0.03, respectively). In fibrinogen values and prothrombin time however, no significant differences were observed (p=0.8, and p=0.3, respectively). Significant differences were not observed between the groups upon evaluation of Lp (a) (group 1: 21.5±17.1 mg/dl; group 2: 15.7±8.5 mg/dl; and group 3: 27.6 ±20 mg/dl; p=0.1).
Conclusion: No marked differences were observed in the Lp (a) serum concentration between the preeclamptic patients and the control group; and it was shown that it was not associated with the severity of the disease.

Key Words: Preeclampsia, Lipoprotein (a), albumin, fibrinogen

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ÖZET

Amaç: Preeklampsi tanısı konulan hastaların serum Lipoprotein (Lp) (a) düzeylerine bakarak, sağlıklı gebelere oranla preeklamptik olgularda Lp (a)' nın yükselip yükselmediğini araştırmak, yüksek Lp(a) konsantrasyonunun preeklampsi şiddetiyle bağlantılı olup olmadığını araştırmaktır.
Yöntem: 28 haftanın üzerindeki 10 hafif preeklamptik (grup 1), 10 ağır preeklamptik (grup 2) ve kontrol grubunu (grup 3) oluşturan 20 normal gebe olmak üzere toplam 40 olgu çalışmaya alındı. Gruplar arasında trombosit, total protein, albumin, fibrinojen, serum Lp (a) değerleri ve prothrombin zamanı karşılaştırıldı.
Bulgular: Üç grup karşılaştırıldığında total protein, albumin ve trombosit değerleri arasında anlamlı fark saptanmıştır (p<0.001, p<0.001, p:0.03). Fibrinojen değerleri ve prothrombin zamanı karşılaştırıldığında ise anlamlı fark izlenmemiştir (p:0.8, p:0.3). Çalışmamızın asıl konusu olan Lp (a) değerlendirildiğinde ise gruplar arasında anlamlı fark izlenmemiştir. (grup 1: 21.5±17.1 mg/dl; grup 2: 15.7±8.5 mg/dl; grup 3: 27.6 ±20 mg/dl; p=0.1)
Sonuç: Preeklamptik hastalar ve kontrol grubunda Lp (a) serum konsantrasyonunda belirgin farklılık izlenmemiştir ve hastalığın şiddetiyle ilişkili olmadığı gösterilmiştir.

Anahtar Sözcükler: Preeklampsi, Lipoprotein (a), albumin, fibrinojen

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INTRODUCTION

Preeclampsia is characterized by hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, arising after the 20th week of pregnancy in women, who were previously normotensive) with proteinuria (≥300 mg/day), or occasionally end-organ damage (1, 2). While the prevalence varies based on geographic regions, socio-economic level or race, the worldwide prevalence varies between 2 and 8% (3). Although mortality rates associated with preeclampsia/eclampsia are gradually decreasing in the developing countries in particular, preeclampsia/eclampsia is maintaining its place among the most frequent causes of maternal mortality together with bleeding (4).

There is no screening test to determine the potential preeclampsia during the routine follow-up of pregnant women. It is therefore seen how important are the early diagnosis, follow-up and treatment of patients diagnosed with preeclampsia.

Despite the studies carried out within long years, the etiology of preeclampsia is not clear yet. Endothelial cellular dysfunction has become important in the pathophysiology of preeclampsia in the recent years (5). Considering the high levels of Lipoprotein (Lp) (a) levels together with the atherosclerotic disease and formation of thrombosis, Lp (a) levels in pregnant women is becoming the focus of attention of researchers.

The objective of this study was to test the serum Lp (a) levels in patients diagnosed with preeclampsia, and to investigate if Lp (a) increases in preeclamptic cases as compare to healthy pregnant women, and if high concentrations of Lp (a) is associated with preeclampsia development and severity of the disease.

MATERIALS and METHODS

In total, 40 cases, out of which 10 with mild preeclampsia and 10 with severe preeclampsia, all past the 28th week of pregnancy and hospitalized SSK Ankara Obstetrics and Gynecology Training and Research Hospital, Perinatology Clinic between October 2001 and January 2002 were included in this study together with 20 women with normal pregnancy.

Cases with arterial blood pressure exceeding 140/90 mmHg in at least two measurements with intervals of six hours, <3+ protein in spot urine or proteinuria in the range of 0.3-5 g in 24-hour urinalysis were accepted as mild preeclampsia (Group 1), and cases with arterial blood pressure exceeding 160/110 mmHg or over, 3+ proteinuria in spot urine or proteinuria exceeding 5 g in 24-hour urinalysis were accepted as severe preeclampsia (Group 2). Patients in both groups were not receiving antihypertensive treatment, and hypertension in history had started in week 25 of pregnancy.

Arterial blood pressure in all the cases constituting the control group (Group 3) were within normal limits, liver function tests were within normal limits, and they had no proteinuria.

Multiple gestation cases, those with internal or medical problems including diabetes mellitus or Early Membrane Rupture (EMR) cases, and cases with chronic hypertension were not included in the study.

Blood (10 cc) was collected from all cases in biochemistry test tubes for Lp (a) measurement. These blood samples were centrifuged under 5000 rpm, and serum was separated. Serum samples obtained from all groups were maintained in the deep freezer in the blood center of our hospital at -70 ˚C. Commercial ELISA kit from Pharmacia firm was used in testing to run Lp (a) levels. Reference range for Lp (a) level was accepted as 2.1-57.3 mg/based on the standardized test. Values exceeding 57.3 mg/were accepted as significantly higher.

Statistical analysis for the study was carried our using the SPSS (Statistical Program for Social Sciences) for Windows package program. Of the continuous variables determined with measurement, the inter-group differences of those with normal distribution were examined with the Student's t-test, and those without normal distribution were examined with Mann-Whitney U-test. The inter-group difference of frequency of classified variables was examined with chi-square test. Differences with probability smaller than 0.05 (p<0.05), were accepted as statistically significant.

RESULTS

Examination of demographic characteristics of 20 control cases, 10 cases with mild preeclampsia and 10 cases with severe preeclampsia showed that the mean maternal age was 31.4±8.6 in the group with mild preeclampsia, 27.9±5.3, in the group with severe preeclampsia and 24±5.3 in the control group. The mean age in the cases with mild preeclampsia and severe preeclampsia were found significantly higher as compared to the control group (p=0.03 and p<0.05, respectively) (Table 1).

In the evaluation regarding the gravida number, the number was 2.4±1.5 in the mild preeclampsia group, 2.7±1.8 in the severe preeclampsia group and 2.2±1.3 in the control group. There were no significant differences between the three groups (p=0.8 and p>0.05, respectively) (Tablo-1). There were no significant differences as regards parity between the three groups (p=0.325 and p>0.05, respectively) (Table-1).

Upon calculation of the gestational weeks based on the last menstruation date (LMD), the number was 37.8±2.1 in the mild preeclamptic group, 33.2±2 in the severe preeclamptic cases, and 36.8±2.6 in the control group. In all the three groups, significant differences in gestational weeks were found based on LMD the severe preeclamptic cases as compared to the control group and the mild preeclamptic group (p=0.007 and p<0.05, respectively) (Table-1).

Table 1: Epidemiologic and obstetric characteristics of the study groups

	Control group n=20	Mild preeclampsia n=10	Severe preeclampsia n=10	p value
Age (years)	24±5.3	31.4±8.6	27.9±5.3	p=0.03
Gravida (n)	2.4±1.5	2.7 ±1.8	2.2±1.3	p=0.8
Parity (n)	%66 primipara %34 multipara	%48 primipara %52 multipara	%64 primipara %36 multipara	p=0.325
Gestational weeks based on LMD (weeks)	36.8±2.6	37.8±2.1	33.2±2	p=0.007

Examination of the distribution of clotting factor levels in cases included in the study showed that the mean maternal platelet value in the control group was 264150±75780 mm³, 246400±62707 mm³ in the mild preeclamptic cases and 175200±73971 mm³ in the severe preeclamptic cases. As regards all the three groups, the difference between the platelet levels in the severe preeclamptic cases and the control group together with the mild trombosit was found significantly different (p=0.03) (Table 2).

When serum protein levels were compared among the three groups, the total protein was 6.4±0.2 gr/dl in the control group, 6±0.4 gr/dl in mild preeclamptic cases and 5.5±0.4 gr/dl in severe preeclamptic cases. Serum total protein level in severe preeclamptic group was found as significantly different (p<0.001 and p<0.05, respectively) (Table 2). Serum albumin levels were found 3.3±0.2 gr/dl in the control group, 2.6±0.3 gr/dl in mild preeclamptic group and 2.3±0.3 gr/dl in severe preeclamptic group. Serum albumin levels were significantly different in mild and severe preeclamptic groups as compared to the control group (p<0.001 and p<0.05, respectively) (Table 2).

Examination of fibrinogen levels showed that the same was 447±106 mg/dl in the control group, 465±78 mg/dl in preeclamptic cases and 448±145 mg/dl in severe preeclamptic cases. No statistically significant differences were found between the three groups as regards the fibrinogen levels in blood (p=0.8 and p>0.05, respectively) (Table 2).

Examination of prothrombin times between the study groups showed that the same was 12.7±1.1 sec. in the control group, 11.9±1.1 sec. in the pregnant women with mild preeclampsia, and 12.5±1.5 sec in the severe preeclamptic group. There were no statistically significant differences between the three groups (p=0.3 and p>0.05, respectively) (Table-2).

Table 2 Comparison of clotting and serum protein levels between the groups

	Control group n=20	Mild preeclampsia n=10	Severe preeclampsia n=10	p value
Platelet (mm³)	264150±75780	246400±62707	175200±73971	p=0.03
Total protein (g/dl)	6.4±0.2	6±0.4	5.5±0.4	p<0.001
Albumin (gr/dl)	3.3±0.2	2.6±0.3	2.3±0.3	p<0.001
Fibrinogen (mg/dl)	447±106	465 ±78	448±145	p=0.8
Prothrombin time (sec)	12.7±1.1	11.9±1.1	12.5±1.5	p=0.3
Lipoprotein (a) (mg/dl)	21.5±17.1	15.7±8.5	27.6 ±20	p=0.1

When the serum Lp (a) levels, which is the main theme of our study are taken in evaluation, it was seen that the level was 21.5±17.1 mg/dl in the control group, 15.7±8.5 mg/dl in the group with mild preeclampsia and 27.6±20 mg/dl in the severe preeclampsia group. Upon statistical evaluation of the three groups, no statistically significant differences were found between groups as regards serum Lp (a) levels (p=0.1 and p>0.05, respectively)(Table 2) (Figure 1).

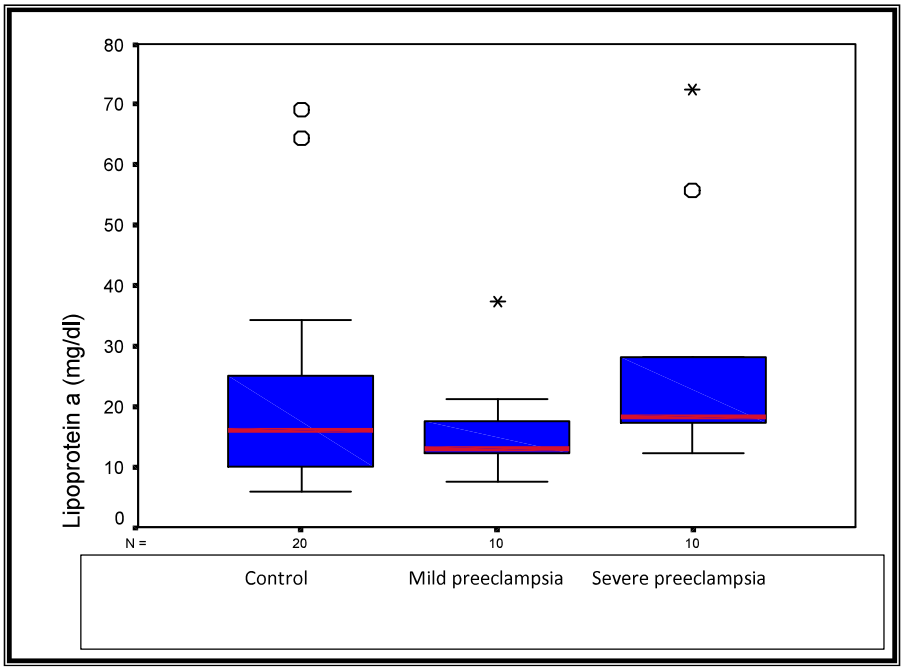

Figure 1: Distribution of Lipoprotein (a) levels between the study groups

DISCUSSION

Preeclampsia is an important cause of fetal growth retardation and fetal and maternal mortality and morbidity. While the prevalence is increasing throughout years, it is found 5% in the average in developed countries (6).

Although pathophysiology of preeclampsia has not been clarified, low placental perfusion is the most common change in preeclampsia. Utero-placental circulation is not like the other normal pregnancies. There is no microcirculation in preeclampsia; instead, spiral arteries deliver blood to the intervillous space (7).

This low perfusion in preeclampsia has been explained with the fibrin and platelet deposition in the placental bed, and development of thrombosis and infarct. In severe cases, in can be encountered with widespread intravascular coagulation together with platelet and fibrin deposition, and multisystem organ involvement including brain, liver and kidneys (8, 9). After all, the cause of all these negative changes in preeclampsia has been attempted to be explained with lesser trophoblastic invasion in myometrial spiral arteries and the development of characteristic lesions named “acute atherosis” forming as a result of endothelial damage (10, 11).

Lp (a) is an independent genetic risk factor for atherogenesis and thrombosis. An association between high levels of Lp (a) and changes in vascular walls was found in many studies resulting in the hypothesis that high levels of Lp (a) causes atherosclerosis. The mechanism for Lp (a) activity resulting in atherogenesis and thrombosis is explained as follows (12);

1-) Slowing down in fibrinolysis and thrombosis effected through the inhibition of plasmin activity because of the similar structural homogeneity between the plasminogen and apolipoprotein (a), which is the carried protein of Lp (a) has been shown

2-) Based on its similar characteristics with the low-density Lp, Lp (a) targets the cholesterol distribution by binding to the probable plasminogen receptors at the side of endothelial damage. Therefore, high levels of Lp (a) can result in excessive cholesterol deposition on vascular wall, and this perhaps results in the formation of atheroma plaques seen in preeclampsia.

Also, it has clearly be shown that the lesser effective invasion of myometrium with trophoblastic cells resulting from the increased immunosuppression ibn spiral arteries, which is known as the etiologic factor in preeclampsia, is a result of the plasmin-mediated activation inhibition of transforming growth factor-β (TGF-β)-like substances (13). In vitro evidences indicate that Lp (a) can inhibit the plasmin-mediated activation of TGF-β (13). Therefore, this has resulted in the idea that high levels of Lp (a) can cause an increase in preeclampsia incidence. Another mechanism suggesting the high levels of Lp (a) as the cause of preeclampsia is the fact that it increases the foam cell formation and atherosis in spiral arterial walls.

In the light of these data, in our study aiming at finding out the relationship between the high levels of Lp (a) and determining the levels of Lp (a) in preeclamptic patients, we found statistically significant differences in maternal

ages (p=0.008) and gestational ages (p<0.05) in the cases in mild preeclampsia (n=10), severe preeclampsia (n=10) and in the control group (n=20).

We found that serum Lp (a) levels exceeded the normal values (57.3 mg/dl) only in 4 patients out of the 40 we have included in the study. Of these 2 were in the control group, and the remaining 2 were in the severe preeclamptic group.

In the study of Maria and colleagues, they found the serum Lp (a) levels, are found higher in preeclamptic patients in proportion with the severity of the disease (14). However, observations that abnormal Lp (a) levels in women with severe preeclampsia and without HELLP syndrome are higher as compare to women with both HELLP syndrome and preeclampsia suggests that preeclampsia with and without HELLP syndrome have different etiologies.

Again, Jian and colleagues who support the togetherness of Lp (a) and preeclampsia, showed in their study that the significant and linear increase in plasma Lp (a) levels were related to the severity of preeclampsia (12). They found that the Lp (a) levels in mild and severe preeclampsia were 5 to 10 folds higher as compared to women with normal pregnancy (12). Wang and colleagues reported that they found higher Lp (a) levels in women with preeclampsia as compared to women who had uncomplicated pregnancies (15).

In contrast with these results, Casper and colleagues found no differences in Lp (a) concentrations between 39 women with preeclampsia and 47 healthy women (13). Naveed and colleagues evaluated the Lp (a) concentration changes between the 10^{th} and 35^{th} gestational weeks with Wilcoxon's sign test in pregnant women between their 10^{th} and 35^{th} weeks they had included in their study group, and found that concentration increased linearly with the increasing gestational week, and reached twice the baseline value at week 35. However, they found no statistically significant changes between the preeclamptic group and the control group. They found the mean Lp (a) value in women with normal pregnancy as 20 mg/dl, and 14 mg/dl in preeclamptic women (16). Balint and colleagues found no statistically significant differences in Lp concentrations between the groups consisting of 51 women with normal pregnancy and 59 pregnant women with severe preeclampsia (16).

The differences between our study and the studies of Wang and colleagues and Jian and colleagues arise from the selection criteria for study groups, because preeclamptic patients with HELLP syndrome and impaired renal functions were included in both studies. As known, although Lp (a) level is under strict genetic regulation, its metabolism is affected from multiple factors. Lp (a) levels are extremely high in patients with chronic renal insufficiency or nephrotic syndrome. The high levels of Lp (a) in the studies of Wang and colleagues and Jian and colleagues can be due to the impairment in renal functions.

Renal function tests of the cases in our study were normal; however, liver enzymes were significantly higher in preeclamptic pregnant women (p=0.007 and p<0.05, respectively). We think that lower values of Lp (a) in cases with liver dysfunction are proportional with our results.

CONCLUSION

In our study we have conducted with the purpose of investigating the importance of serum Lp (a) levels in determining the diagnosis, ethiopathogenesis and prognosis of the disease in preeclampsia serum Lp levels and other biochemical parameters were determined and compared with each other in the control group of 20 cases, 10 mild preeclamptic cases and 10 severe preeclamptic cases.

In conclusion, no marked differences were found in serum Lp (a) concentrations between the preeclamptic patients and the controls, and it was shown that Lp (a) is not associated with the severity of the disease.

Conflict of interest

No conflict of interest was declared by the authors.

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