

High-Density Lipoprotein Cholesterol May Discriminate Mild and Severe Preeclampsia

Esra CAN¹, Mehmet Mustafa CAN², İbrahim Halil TANBOĞA³, Oluş APİ¹, Murat BİTEKER⁴, Orhan ÜNAL¹

İstanbul, Turkey

OBJECTIVE: Low serum levels of high-density lipoprotein (HDL) cholesterol have been found to be associated with the severity of the inflammatory disorders. Moreover; it has been shown that preeclampsia is a disorder of immune system with predominant involvement of proinflammatory molecules. Therefore the purpose of the present study was to assess whether blood serum HDL cholesterol levels could be used as a predictor of the severity of preeclampsia.

STUDY DESIGN: Forty women with preeclampsia were recruited and thirty-five normal pregnant women were matched for both maternal age and gestational age served as control. The materials were collected immediately after delivery of the fetus, before placenta expulsion and before clumping of the umbilical cord in patients and controls whom were in fasting state. Total cholesterol, HDL cholesterol, triglyceride (TG) and low-density lipoprotein (LDL) cholesterol levels were assessed.

RESULTS: Among the preeclamptic women, 12 were diagnosed with severe preeclampsia and 28 mild. There were no statistically significant differences between preeclampsia and normal pregnancy except when divided by according to systolic and diastolic blood pressure, proteinuria levels, parity, and HDL cholesterol levels. Of the women with preeclampsia (n=40), 30 % had severe disease. Women with mild and severe preeclampsia had significantly higher blood pressures at delivery and earlier gestational ages in comparison to control subjects. Although TG, VLDL and LDL levels ($p>0.05$) were comparable between preeclampsia and normal pregnancies, HDL cholesterol levels were significantly lower in patients with preeclampsia. Moreover, in subgroup analysis, patients with severe preeclampsia had the lower HDL levels ($p<0.05$) in comparison with mild preeclampsia.

CONCLUSIONS: Blood HDL cholesterol levels measured at delivery were reduced in patients with preeclampsia, and patients with reduced levels of HDL cholesterol had a substantially higher probability of the disease severity in comparison to those with mild preeclampsia or those controls.

Key Words: Preeclampsia, HDL cholesterol, Disease severity

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Introduction

Preeclampsia is the most important causes of maternal and neonatal mortality and morbidity in pregnancy.¹ Although the causes of preeclampsia are completely unknown, one of the responsible mechanisms is thought to be activation of immune systems with predominant involvement of cytokines and

chemokines.^{2,3} Cytokines which are the one of the important sources of inflammatory mediators have emerged as key cellular determinants of progression of the preeclampsia.⁴ Recent studies have shown that cytokines which mediate the immune response to inflammatory disorders, cause observed changes in lipid metabolism.⁵ Infections and inflammation induce the cytokines, which produce a variety of changes in the plasma concentrations of lipids and lipoproteins and it has been shown that there is a marked decrease and dysfunctional serum high density lipoprotein (HDL) cholesterol levels during inflammatory disorders and other infections.⁶⁻⁹ Furthermore, low serum HDL cholesterol levels have been found to be associated with the severity of disease and poor prognosis.⁸⁻¹¹ On the basis of these facts, level of HDL cholesterol may be a result of processes causing preeclampsia. However, the prognostic role of blood HDL cholesterol levels in preeclampsia has not been investigated previously. The purpose of the present study was to assess whether blood serum HDL cholesterol levels could be used as a predictor of the severity of preeclampsia.

¹Kartal Lütfi Kırdar Research and Education Hospital Obstetrics and Gynecology Department, Istanbul

²GMMA, Haydarpaşa Training Hospital Cardiology Department, Istanbul

³Erzurum State and Education Research Hospital Cardiology Department, Erzurum

⁴Haydarpaşa Training Hospital Cardiology Department, Istanbul

Address of Correspondence: Mehmet Mustafa Can
GMMA, Haydarpaşa Training Hospital
Cardiology Department, Istanbul
mehmetmustafacan@yahoo.com

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Material and Method

Subjects

The study has been approved by the Local Institutional Review Board and an informed written consent was obtained from each study participant before inclusion. In the current investigation, 40 women with preeclampsia were recruited and 35 normal pregnant women were matched for both maternal age and gestational age served as control. Among the preeclamptic women, 12 were diagnosed with severe preeclampsia and 28 mild. Preeclampsia was diagnosed and classified according to strict criteria recommended by American College of Obstetricians and Gynecologists in 2002: a systolic blood pressure of 140 mmHg or higher or a diastolic blood pressure of 90 mmHg or higher on two occasions at least 6h apart occurring after 20 weeks of gestation in a pregnant woman with previously normal blood pressure and detectable urinary protein (>1+ by dipstick or 0.3 g/24 h and more).¹² Clinical features of patients with severe preeclampsia (if any) were included as a blood pressure greater than or equal to 160 mmHg/110 mmHg with either a urine dipstick showing 3+ or 4+ in a random urine sample or greater than 5 g of proteinuria over 24 h. Other evidence of severe disease included serum creatinine, eclampsia, pulmonary edema, oliguria (less than 500 ml/24 h), fetal growth restriction, oligohydramnios and symptoms suggesting significant end-organ involvement (headache, visual disturbance). Women who met the criteria of preeclampsia but not severe preeclampsia were diagnosed as mild preeclampsia. Exclusion criteria were previous lipid metabolism disorders, history of dyslipidemia, multiple gestation, diabetes mellitus, chronic hypertension, infectious diseases diagnosed in pregnancy, premature rupture of membrane, active labor, polyhydramnios, kidney diseases and signs of other concurrent medical complications. The control subjects had no sign of any gestational complication and fetal distress without evidence of hypertension or proteinuria and all gave health neonates of appropriate size for gestational age.

Sample collection and analysis

The materials were collected immediately after delivery of the fetus in patients and controls whom were in fasting state. Maternal venous blood was obtained in by puncturing the antecubital vein. Total cholesterol, HDL cholesterol, and triglyceride levels (TG) were measured on an autoanalyzer of the Konelab 60i analyzer (Konelab, Espoo, Finland). Low density lipoprotein was calculated using Friedelwald's Formula.¹³

Statistical analysis

Continuous variables are expressed as mean \pm SD. The level of significance was 0.05. The Kolmogorov-Smirnov test was used for the normality test of all variables. To compare differences between patients with or without disease severity, Mann-Whitney U and Fisher's exact tests were used for continuous and categorical variables, as appropriate. Statistical analysis were performed using SPSS, version 15.0 for Windows.

Results

Baseline clinical and demographic characteristics of our study population are given in **Table 1 and 2**. There were no statistically significant differences between with preeclampsia and normal pregnancy except when divided by according to systolic and diastolic blood pressure, proteinuria levels, parity, and HDL cholesterol levels. Of the women with preeclampsia (n=40), 30 % had severe disease. Women with mild and severe preeclampsia had significantly higher blood pressures at delivery and earlier gestational ages in comparison to control subjects. Although TG, very low density lipoprotein (VLDL) and LDL levels ($p>0.05$) were comparable between preeclampsia and normal pregnancies, HDL cholesterol levels were significantly lower in patients with preeclampsia. Moreover, in subgroup analysis, patients with severe preeclampsia had the lower HDL levels ($p<0.05$) in comparison with mild preeclampsia.

Table 1: Baseline characteristics of pregnant women with preeclampsia and those without preeclampsia.

Variables	Controls n (35)	Preeclampsia n (40)	p value
Maternal age (y) ^a	32 \pm 3	34 \pm 3	0.1
Systolic BP(mmHg) ^a	104 \pm 8	154 \pm 20	0.0001
BP(mmHg) ^a	72 \pm 9	99 \pm 8	0.0001
GA at delivery (weeks) ^a	251 \pm 19	248 \pm 23	0.08
Proteinuria (mg) ^a	108 \pm 32	1117 \pm 667	0.0001
Total cholesterol(mg/dl) ^a	167 \pm 40	180 \pm 49	0.2
HDL cholesterol (mg/dl) ^a	45 \pm 13	35 \pm 11	0.002
LDL cholesterol (mg/dl) ^a	98 \pm 35	113 \pm 42	0.1
Triglyceride (mg/dl) ^a	118 \pm 52	147 \pm 73	0.06
VLDL cholesterol (mg/dl) ^a	23 \pm 10	29 \pm 14	0.06

^a: Values are mean \pm SD. **BP**: blood pressure, **GA**: Gestational age, **y**: year, **n**: number, **HDL**: high density lipoprotein, **LDL**: low density lipoprotein, **VLDL**: very low density lipoprotein

Table 2: Baseline characteristics of pregnant women with mild and severe preeclampsia.

Variables	Mild Preeclampsia (28)	Severe Preeclampsia n (12)	p value
Maternal age (y) ^a	31±3	33±3	0.1
Systolic BP(mmHg) ^a	141±7	167±20	0.01
Diastolic BP(mmHg) ^a	99±7	99±10	0.8
GA at delivery (weeks) ^a	245±23	244±19	0.12
Proteinuria (mg) ^a	621±127	1613±639	0.0001
Total cholesterol(mg/dl) ^a	166±40	174±46	0.65
HDL cholesterol (mg/dl) ^a	37±7	30±10	0.03
LDL cholesterol (mg/dl) ^a	100±32	109±41	0.52
Triglyceride (mg/dl) ^a	142±75	147±86	0.85
VLDL cholesterol (mg/dl) ^a	28±15	29±17	0.85

^a: Values are mean ± SD. **BP**: blood pressure, **GA**: gestational age, **y**: year, **n**: number, **HDL**: high density lipoprotein, **LDL**: low density lipoprotein, **VLDL**: very low density lipoprotein

Discussion

The main findings of our study were that¹ blood HDL cholesterol levels measured at delivery were reduced in patients with preeclampsia, and ² patients with low levels of HDL cholesterol had a substantially higher probability of the disease severity in comparison to those with mild preeclampsia or those controls. Preeclampsia is a disorder of immune system with predominant involvement of proinflammatory molecules.¹⁴⁻¹⁵ The pathophysiology of the disease involves impaired trophoblast invasion, alteration of immune tolerance and also exaggeration of the systemic inflammatory process. Previous articles alerted the scientific community that hyperactivation of cytokines and adhesion molecules which were concordance with the severity of disease may give prognostic data about the severity of the disease.¹⁶ It has been shown that low HDL cholesterol could be as a prognostic factor for severe inflammatory disorders^{7-9,17-19} There are several pathogenic mechanisms were thought to be the causative role for the association between low HDL levels and the severity of the disease. High concentrations of proinflammatory cytokines of which suppress lipoprotein production during infections were found to have a role in low HDL cholesterol level. Furthermore, previous articles dictated that serum HDL cholesterol levels have a negative correlation with concentrations of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-alfa in severe sepsis.⁸ We conducted this study in the experimental setting, and applied observational design, therefore, not drawing any definite pathophysiologic mechanisms for the association between low serum HDL cholesterol level and the severity of preeclampsia. We speculate that the similar mechanisms may be attributable for the decrease in serum HDL cholesterol level in preeclampsia and the other inflammatory disorders. Indeed, serum lipids during gestation are different between normotensive and preeclamptic women. Baker et al. reported

women with mild preeclampsia had higher total cholesterol to HDL ratio than control subjects.²⁰ Moreover, they dictated that patients with severe preeclampsia had less atherogenic profile than those controls, suggesting that lipid profile is a risk factor for only mild variant of preeclampsia and severe and mild preeclampsia may be pathologically different. Our data provides insight to this conflicting data. It is shown that although the patients and controls have similar TG, LDL and VLDL levels, patients have lower HDL level than those controls, and it should not be expected to have higher lipid profiles as the disease get worsen. Moreover, lower HDL could be used as a predictor of the disease severity in patients with preeclampsia. There are a few limitations of the study worth mentioning. Although compatible in size with other similar investigations, this study was performed in a relatively small cohort, so chance represents a plausible alternative explanation. Many potentially important biomarkers and cytokines of preeclampsia indices were not measured in the index study. We used a cross-sectional study design and therefore, predictor of preeclampsia during follow period of pregnancy with serial lipid profile measurements were not studied and included only patients whose lipid profile were normal before pregnancy. Finally, our study is too small, and observational design preclude us to adequately assess these important links. These data most certainly should be confirmed in a larger, randomized trial.

Yüksek Dansiteli Lipoprotein Kolesterol Ciddi ve Hafif Preeklampsiyi Ayırabilir

GİRİŞ: Düşük yüksek dansiteli lipoprotein (HDL) düzeyi ile inflamasyonun ciddiyeti arasındaki ilişki bilinmektedir. Preeklampsinin de proinflatuar moleküllerin öncülük ettiği immün sistem hastalığı olduğu gösterilmiştir. Çalışmamızın amacı kan HDL seviyelerinin preeklampsinin ciddiyetini belirlemedeki rolünü araştırmaktır.

GEREÇ VE YÖNTEM: Yaş ve gestasyonel yaş bakımından benzer preeklampsi tanısı almış 40 ve 35 sağlıklı gebe çalışmaya dahil edildi. Kan örnekleri fetusun doğumundan hemen sonra umbilikal kord bağlanmadan önce toplandı. Total kolesterol, HDL kolesterol, trigliserid ve düşük dansiteli lipoprotein seviyelerine bakıldı.

BULGULAR: Preeklampitik hastaların 12'si ağır, 28'i hafif idi. Hasta grupları arasında sistolik ve diyastolik kan basıncı, proteinürü seviyesi, parite, HDL kolesterol düzeyleri hariç aralarında anlamlı fark saptanmadı. Ağır ve hafif preeklampitik hastalar kontrol grubuna göre daha yüksek kan basınçlarına ve erken gestasyonel yaşa sahiptiler. Preeklampitik hastalar ve kontrol grubunda benzer TG, VLDL and LDL düzeyleri olmasına rağmen ($p>0,05$), HDL düzeyleri preeklampitik hastalarda anlamlı derecede düşüktü ($p<0,05$). Daha da ötesi alt grup analizinde ağır preeklampitik hastalar hafif preeklampitik hastalara göre daha düşük HDL seviyelerine sahipti ($p<0,05$).

SONUÇ: Doğum sırasında ölçülen kan HDL kolesterol düzeyleri preeklampitik bayanlarda azalmıştır ve azalmış HDL kolesterol düzeyleri hastalığın ciddiyeti ile ilişkilidir.

Anahtar Kelimeler: Preeklampsi, HDL kolesterol, Hastalık ciddiyeti

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