

# The Analysis of Serum Calcium and Urine Calcium/Creatinine Ratio in Diagnosis of Preeclampsia

## Preeklampsi Tanısında Serum Kalsiyum ve İdrar Kalsiyum/Kreatinin Oranının Analizi

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### Abstract

**Objective:** Preeclampsia is one of the primary reasons for maternal and fetal morbidity and mortality. Maternal and fetal complications can be prevented by early diagnosis, treatment, and follow-up of preeclampsia. This study aimed to determine the clinical diagnostic value of serum calcium (Ca) levels and urinary calcium/creatinine (Ca/cr) ratio in preeclampsia.

**Method:** A retrospective study was conducted on a sample population of 183 pregnant patients diagnosed with preeclampsia who delivered singleton babies at the Clinic of Obstetrics and Gynecology, University of Health Sciences Turkey, Şişli Etfal Training and Research Hospital, İstanbul, Turkey, between January 2010 and January 2012. The patients were divided into two groups. Group 1: Preeclampsia; group 2: Preeclampsia with severe features. Serum Ca levels and urinary Ca/cr ratios of the patients were evaluated and compared.

**Results:** Hypocalcemia rates were higher in group 2 (93%) than in group 1 (58%). There was a statistically significant difference between the distribution of patients in the two groups according to serum Ca levels (28.339; 1; p=0.0001). The urinary Ca/cr ratios were lower in group 2 due to the decreased Ca extraction (58.481; 1; p<0.0001). The mean Ca/cr ratio was 0.032 in group 2 and 0.11 in group 1.

**Conclusion:** Low serum Ca levels were detected in preeclamptic patients, and as the severity of preeclampsia increased, the Ca/cr ratio decreased due to decreased urinary Ca excretion. These findings were more significant for group 1; however, beyond a certain threshold, lower serum Ca levels and urinary Ca/cr ratio did not diagnose preeclampsia with severe features in group 2.

**Keywords:** Preeclampsia, serum calcium, urinary calcium/creatinine ratio

### Öz

**Amaç:** Preeklampsi maternal ve fetal morbidite ve mortalitenin önde gelen nedenlerinden biridir. Erken tanı, tedavi ve takibi ile gelişebilecek maternal ve fetal komplikasyonlar önlenebilir. Bu çalışma, preeklampside serum kalsiyum (Ca) düzeyleri ve idrar kalsiyum/kreatinin (Ca/cr) oranının klinik tanısai değerini belirlemeyi amaçlamaktadır.

**Yöntem:** Ocak 2010 ile Ocak 2012 tarihleri arasında Sağlık Bilimleri Üniversitesi, Şişli Etfal Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde preeklampsi tanısı alan ve tekiz gebeliği bulunup doğum yapan 183 gebe hasta üzerinden retrospektif bir çalışma yapılmıştır. Hastalar iki gruba ayrıldılar. Grup 1: Preeklampsi; grup 2: Şiddetli özelliklere sahip preeklampsi. Hastaların serum Ca seviyeleri ve idrar Ca/cr oranları değerlendirildi ve karşılaştırıldı.

**Bulgular:** Hipokalsemi oranları grup 2'de (%93), Grup 1'e (%58) göre daha yüksekti. Serum Ca düzeylerine göre iki gruptaki hastaların dağılımı arasında istatistiksel olarak anlamlı fark vardı (28.339; 1; p=0,0001). Grup 2'de Ca ekstraksiyonundaki azalma nedeniyle idrar Ca/cr oranları daha düşüktü (58.481; 1; p<0,0001). Ortalama Ca/cr oranı grup 2'de 0.032 ve grup 1'de 0,11 idi.

**Sonuç:** Preeklamptik hastalarda düşük serum Ca düzeyleri saptandı ve preeklampsinin şiddeti arttıkça idrarla Ca atılımının azalmasına bağlı olarak Ca/cr oranı azaldı. Bu bulgular grup 1 için daha anlamlıydı; ancak, belirli bir eşik ötesinde, düşük serum Ca seviyeleri ve idr Ca/cr oranı grup 2'de şiddetli özelliklere sahip preeklampsiyi teşhis edemedi.

**Anahtar kelimeler:** İdrar kalsiyum/kreatinin oranı, preeklampsi, serum kalsiyumu



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## Introduction

Preeclampsia, a multisystemic condition caused by placental and maternal vascular dysfunction, is seen in an average of 4.6% of all pregnancies worldwide (1). 10-15% of maternal mortality due to complications during pregnancy is related to preeclampsia/eclampsia (2). Preeclampsia can cause serious complications that can affect many organ systems and result in end-organ dysfunction. Maternal and fetal complications of preeclampsia can be avoided or limited by early identification of at-risk pregnancies.

Preeclampsia is described as new-onset hypertension; systolic blood pressure of  $\geq 140$  mmHg and diastolic blood pressure of  $\geq 90$  mmHg or both, after 20 weeks of gestation in a previously normotensive patient, with or without proteinuria. The following of the criterias can list in the absence of proteinuria: Thrombocytopenia; platelet count  $< 100,000/\mu\text{L}$ , renal failure; serum creatinine levels above 1.1 mg/dL or a doubling of the serum creatinine levels in the absence of other renal diseases, hepatic dysfunction; elevation of serum hepatic transaminases to twice the normal concentration, pulmonary edema, new-beginning headache unrelieved with medications and not unexplained with a different diagnose or visual symptoms (3).

Preeclampsia with severe features is characterized by systolic blood pressure of  $\geq 160$  mmHg or diastolic blood pressure of  $\geq 110$  mmHg or both. The other criterias as follows: Thrombocytopenia; platelet count  $< 100,000/\mu\text{L}$ , hepatic dysfunction, unexplained by a different diagnosis; the elevation of serum hepatic transaminases to twice the normal concentration or by severe right upper quadrant or epigastric pain that can not be relieved with medications, renal failure; serum creatinine levels above 1.1 mg/dL or a doubling of the serum creatinine levels in the absence of another renal disease, pulmonary edema, new-beginning headache unrelieved with medications and unexplained by a different diagnose, visual disturbances (3).

Many physiological changes occur during pregnancy. One of these is the increased renal glomerular filtration rate in the kidneys and consequent increased urinary calcium (Ca) excretion (4). The normal range for 24-hour Ca urine excretion in women is 100 to 250 mg/day. It increases to 350-620 mg/day during pregnancy, but renal ionized Ca excretion considerably decreases in preeclampsia (5).

Various methods and tests based on Ca metabolic changes have been investigated for the early diagnosis or prediction of preeclampsia. Studies such as Ca supplementation, evaluation of serum Ca, urinary Ca, urinary calcium/

creatinine (Ca/cr) levels in preeclamptic and normotensive patients, ionized calcium studies in the umbilical cord, and the Ca-ATPase activity of plasma membranes from human myometrium have been performed on preeclamptic patients. Some studies observed significant findings, while others did not. In addition, some study sample sizes were not extensive enough.

However, the relationship between Ca metabolism and preeclampsia is still unclear. Our study evaluated serum Ca and urinary Ca/cr ratios, whose diagnostic value is still controversial in predicting preeclampsia. This study aimed to analyze the diagnostic value of serum Ca and urinary Ca/cr ratios in preeclampsia.

## Materials and Methods

This retrospective study included 183 pregnant patients who were diagnosed with preeclampsia and delivered singleton babies at the Clinic of Obstetrics and Gynecology, University of Health Sciences Turkey, Şişli Etfal Training and Research Hospital, İstanbul, Turkey between January 2010 and January 2012. Due to its retrospective design, this study was considered exempt from clinical studies ethics committee approval.

Preeclampsia was diagnosed based on new-onset hypertension after 20 weeks of gestation with or without proteinuria. Patients with any of the following features in the absence of proteinuria were diagnosed with preeclampsia: Thrombocytopenia; platelet count  $< 100,000/\mu\text{L}$ , renal failure; serum creatinine levels above 1.1 mg/dL or a doubling of the serum creatinine levels in the absence of other renal diseases, hepatic dysfunction; elevation of serum hepatic transaminases to twice the normal concentration, pulmonary edema, new-beginning headache unrelieved with medications and not unexplained with a different diagnose or visual symptoms (3).

Patients were divided into two groups based on their hypertension. Patients with systolic blood pressure  $\geq 160$  mmHg and diastolic blood pressure  $\geq 110$  mmHg were diagnosed as preeclampsia with severe features and added to group 2. Group 1: Preeclampsia; group 2: Preeclampsia with severe features. Patients with chronic hypertension, diabetes mellitus, urinary infection, renal disease, or multifetal pregnancy were excluded from the study.

Age, gravidity, parity, a gestational week at birth, fetal birth weight, and delivery type (cesarean or vaginal delivery) of eligible patients were recorded. The patient's serum Ca, 24-hour urine protein, Ca, and creatinine values were also

recorded. Hypocalcemia was defined as a serum Ca level of less than 8.8 mg/dL, with a normal range defined as 8.8-10.7 mg/dL. A standard reference interval for the urine Ca (mg/dL)/urine creatinine (mg/dL) ratio is <0.14. Due to possible changes in glomerular filtration, Ca/cr ratio in the 24-h urine specimens was measured instead of the urine's direct Ca concentration. The serum Ca and urinary Ca/cr ratios were evaluated and compared in both groups.

### Statistical Analysis

The Power Analysis method was applied with the GPower 3.1.9.7 program to examine the adequacy of the sample size of the study. When the power (1-β) value is 0.80, and the α value is taken as 0.05, it is concluded that the minimum sample size for serum Ca analysis should be 24 and the minimum sample size for urinary Ca/cr analysis should be 75. Overall, there are 183 pregnant patients in the study, which is a sufficient sample size to have statistical power for both variables.

SPSS Version 18.0 for Windows was used for statistical analysis. The means, standard deviations, frequencies, and correlations of patient demographic variables were calculated. The statistical significance of serum Ca and urinary Ca/cr was evaluated by using an independent two-sample t-test (two-sided). According to the result of the t-test of serum calcium, the effect size is 1.16, and it is the large effect size according to the criterion of Cohen's d (6). Besides, urinary Ca/cr has a large effect size according to the criterion of Cohen's d by 0.87 (6).

With a 95% confidence interval, values of p<0.05, t-test

results were accepted as being statistically significant. For determining the predictive threshold value of urinary Ca/cr ratio in the development of preeclampsia, the "receiver operating characteristic curve (ROC)" was used. Negative and positive predictive values were calculated using the cross tables.

### Results

A total of 183 pregnant patients with preeclampsia were included in the study. Group 1 included 100 (54.6%) patients, while group 2 included 83 patients (45.4%). No significant differences were observed regarding age, gravidity and parity between groups. However, gestational age at delivery and fetal birth weight were significantly lower in group 2 than in group 1. While the rate of cesarean delivery was higher in group 2 (78%), the rate of vaginal delivery was higher in group 1 (58%).

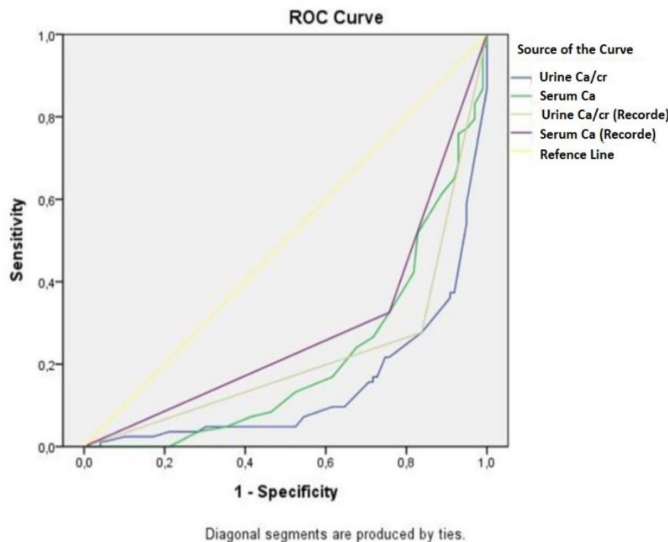
There was an inverse relationship between serum Ca and urinary Ca/cr ratios in preeclampsia. In this study, serum Ca levels were low in 73.8% of patients, whereas 26.2% had a serum Ca level within the normal reference range. The average serum Ca level was 8.5 mg/dL in group 1 and 7.9 mg/dL in group 2. There was a statistically significant difference in serum Ca levels between the groups (28.339;1; p<0.0001). Hypocalcemia was more prevalent in group 2 (93%) than in group 1 (58%). There was also a statistically significant difference between the two groups concerning the urinary Ca/cr ratio (58.481;1; p<0.0001). Ca extraction was lower in group 2 (72%) than in group 1 (16%). The mean Ca/cr ratio was 0.032 in group 2 and 0.11 in group 1 (Table 1).

**Table 1. Baseline demographic features and distribution of the patients between group-1 and group-2 preeclampsia**

	Group 1 preeclampsia (n=100)	Group 2 preeclampsia (n=83)	Total (n=183)	p-value*
<b>Age (years)</b>	29.6±6.1	28.43±6.64	29.1±6.3	
<b>Gravidity</b>	1.7±0.98	1.59±0.86	1.64±0.92	
<b>Parity</b>	1.34±0.89	1.2±0.92	1.27±0.90	
<b>Gestational age (weeks)</b>	35±3.9	33.94±3.76	34.5±3.8	
<b>Fetal birth weight (gr)</b>	2400±800	2100±700	2200±800	
<b>Proteinuria (mg/24 hours)</b>	871.9±443.5	4727.18±2643.42	2620.5±2638.02	
<b>Serum calcium (mg/dL)</b>	8.58±0.6	7.9±0.57	8.27±0.67	<0.0001
<b>Urinary calcium/creatinine</b>	0.11±0.12	0.032±0.04	0.07±0.10	<0.0001
<b>Hypocalcemia</b>	58 (58%)	77 (93%)	135 (74%)	
<b>Low urinary Ca/cr</b>	16 (16%)	60 (72%)	76 (42%)	
<b>High urinary Ca/cr</b>	83 (84%)	23 (28%)	106 (58%)	
<b>Delivery mode (n)</b>				
Caesarian section	42 (42%)	65 (78%)		
Vaginal delivery	58 (58%)	18 (12%)		

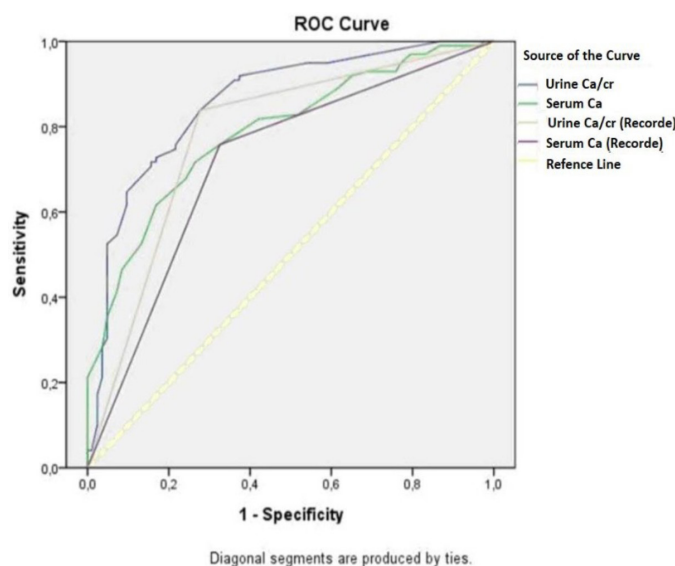
\* Two-sample t-tests (two-sided) were applied, Ca/cr: Calcium/creatinine

On the ROC curve for group 1, the sensitivity to diagnose preeclampsia was more significant. The serum Ca and urinary Ca/cr ratios were more diagnostic of preeclampsia for group 1 (Figure 1). Specificity was more significant on the ROC curve for group 2, and serum Ca and urinary Ca/cr ratios did not diagnose the development of preeclampsia with severe features in group 2. The cut-off point for urinary Ca/cr was 0.35, whereas serum Ca was 8.1 (Figure 2).



**Figure 1.** The ROC curve for group 1, sensitivity and specificity for the diagnosis of preeclampsia

*Ca/cr: Calcium/creatinine, ROC: Receiver operating characteristic*



**Figure 2.** The ROC curve for group 2, sensitivity and specificity for the diagnosis of preeclampsia

*Ca/cr: Calcium/creatinine, ROC: Receiver operating characteristic*

## Discussion

Many studies have been conducted to investigate how maternal serum Ca levels can be used for the early diagnosis and prevention of preeclampsia. The role of Ca in the development of hypertension emphasizes the circulatory and vascular bioactive factors that affect hypertension and draws attention to the quantity and activity of mediators secreted by the endothelium, vascular smooth muscle, and extracellular matrix during pregnancy. Researchers have stressed the importance of intracellular free Ca concentration, which controls smooth muscle contraction and the subsequent chain of activation (7).

Some studies have demonstrated that low serum Ca level are associated with greater preeclampsia risk. Punthumapol and Kittichotpanich (8), and Tuli et al. (9) reported that serum Ca levels were remarkably decreased in preeclamptic women compared to normotensive patients. Seely et al. (10) studied serum and urinary Ca levels in third-trimester preeclampsia and normotensive pregnancies and revealed that preeclamptic pregnancies had lower serum Ca values than normotensives. In addition, Jain et al. (7) compared the serum Ca levels between normal, mild and severe preeclamptic patients and determined that serum Ca levels decreased even more as the severity of preeclampsia increased.

In our study, serum Ca levels decreased by 73.8% and remained within the normal range for 26.2% of preeclamptic patients. We observed a statistically significant difference in serum Ca levels between group 1 and group 2, with average values of 8.58 mg/dL and 7.9 mg/dL, respectively.

Despite these results, some studies have not found an association between hypocalcemia and preeclampsia. Darkwa et al. (11) reported that serum Ca levels did not differ in preeclamptic patients compared to non-preeclamptic patients. Wadhvani et al. (12) studied maternal serum Ca levels from early pregnancy until delivery and cord levels in women with preeclampsia and compared them to normotensive patients. They observed that Ca levels were similar between the groups at all time points (12).

Studies have been published showing that renal Ca extraction decreases with the development of preeclampsia. Sanchez-Ramos et al. (4) observed that preeclamptic patients had less excretion of total calcium than normotensives and gestational hypertension patients. Sirohiwai et al. (13) reported that urinary Ca excretion was remarkably lower in preeclamptic patients than in normotensives and stated that a drop in 24-

hour urinary Ca and a rise in protein are risk factors for preeclampsia. Seely et al. (10) measured preeclamptic and normotensive women's urinary Ca levels in the third- trimester and confirmed that preeclamptic patients have relative hypocalciuria. A meta-analysis reported that urinary Ca excretion was lower in women with preeclampsia than in normotensive pregnancies. However, as the severity of pregnancy-related hypertensive disorders increases, urinary Ca excretion decreases; however, this same decrease is not observed in non-pregnancy-related hypertension (14). Rodriguez et al. (15) examined the Ca/cr ratio in spot urine from normal pregnant women. Subsequently, preeclampsia developed in an average of 80% of the patients with low Ca/cr values. Therefore, their study remarked that the Ca/Cr ratio could be a helpful screening test in predicting preeclampsia (15). Also, Vahdat et al. (16) performed a prospective study to evaluate the predictive value of Ca/cr ratio in preeclamptic patients. In their study, the mean Ca/cr ratio was significantly lower in preeclamptic women and suggested that it may be used as a screening test (16).

However, Saudan et al. (17) found that hypocalciuria precedes the onset of preeclampsia in gestational hypertensive women, and Ca/cr was not sensitive enough to be proposed as a screening test for preeclampsia. Ibrahim et al. (18) conducted a prospective case-control study to determine the predictive value of the Ca/cr ratio in the 24-h urine sample in predicting preeclampsia in pregnant women between 24-34 weeks. They found that the role of Ca/cr ratio in predicting preeclampsia was lower than that of proteinuria and uric acid (18). Also, Ingec et al. (19) reported that urinary Ca excretion was reduced in severe preeclamptic and eclamptic patients, but it cannot be used to identify or predict the severity of preeclampsia.

In our study, we also observed a decrease in urinary Ca, especially in group 2 patients; 72% had hypocalciuria. The mean urinary Ca/cr ratio was 0.032. There is seen statistically significant differences in the urinary Ca/cr ratio in 24-h urine specimens between the two groups (58.481;1; p<0.0001). Ca excretion was reduced significantly in group 2, but the urinary Ca/cr ratio did not diagnose severe preeclampsia on the ROC curve. Therefore, the cut-off point for urinary Ca/Cr was 0.35.

## Conclusion

Low serum Ca levels and decreased urinary Ca excretion were detected in preeclamptic patients. The serum Ca levels and urinary Ca/cr ratios were more likely to diagnose preeclampsia in group 1.

However, we were not able to diagnose the eventual severity of preeclampsia in group 2 using this method. Further studies with more extensive sample sizes are required to confirm and validate the diagnostic value of serum Ca and urinary Ca/cr for preeclampsia.

## Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Our study is retrospective and was carried out on data processing data without using patient names.

**Peer-review:** Internally peer-reviewed.

## Authorship Contributions

Concept: E.B., S.Ö., Design: E.B., S.Ö., Data Collection or Processing: E.B., Analysis or Interpretation: E.B., S.Ö., Drafting Manuscript: E.B., Critical Revision of Manuscript: S.Ö., Writing: E.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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