Persistence of Cardiovascular Risk Factors in Women With Previous Preeclampsia: A Long-term Follow-up Study

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Background: Preeclampsia is a cardiovascular (CV) disease risk factor, and lifestyle modifications are recommended. It was suggested that preeclampsia may increase the prevalence of various CV disease risk factors such as metabolic syndrome, hypertension, insulin resistance, microalbuminuria, and endothelial dysfunction, among others. Here, we investigate the role of serum uric acid in preeclampsia in the development of CV complications.

Materials and Methods: This was an observational case-control study that compared women with history of preeclampsia (n = 25) with age-matched controls with uncomplicated pregnancies (n = 20) who were followed for at least 5 years. Measurements included clinical and ambulatory blood pressure monitoring, ultrasound-measured flow-mediated dilatation (FMD), microalbuminuria, carotid intima-media thickness (CIMT) and serum uric acid, as well as clinical and demographic features. Cardiovascular disease risk factors were compared in women with and without previous preeclampsia.

Results: At the time of index gestation, preeclamptic women had higher serum uric acid values (4.36 ± 0.61 vs 2.27 ± 0.38 mg/dL, $P < 0.001$). Five years after pregnancy, the patients who had preeclampsia were more likely to have hypertension and had higher serum uric acid levels, higher microalbuminuria and CIMT levels, and lower FMD values than did the patients who did not have preeclampsia. The 2 groups were similar with regard to various ambulatory blood pressure parameters. Univariate associates of FMD were history of preeclampsia and the current hypertension status. Microalbuminuria correlated with gestational uric acid levels (coefficient of correlation of 0.40, $P = 0.01$ for FMD and coefficient of correlation of 0.37, $P = 0.01$ for CIMT, respectively).

Conclusions: Preeclampsia might be a risk factor for the development of cardiovascular risk factors at least 5 years after index pregnancy. Serum uric acid and microalbuminuria may be mechanistic mediators of heightened risk, along with impaired endothelial function in preeclampsia.

Key Words: preeclampsia, cardiovascular disease, risk factor, endothelial dysfunction, uric acid, microalbuminuria

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Preeclampsia is a multisystem disorder characterized by maternal endothelial dysfunction. The disease is characterized by hypertension, proteinuria, and edema that develop after 20 weeks of gestation. Preeclampsia complicates 2% to 8% of all pregnancies and is associated with increased morbidity and immediate mortality of both the mother and the fetus.[1] Women with preeclampsia have increased long-term risks for developing hypertension and cardiovascular (CV) disease.[2,3] Thus, preeclampsia is a CV disease risk factor, and women with a history of preeclampsia are recommended to undergo lifestyle modification to reduce CV disease risk.[4]

Several studies have evaluated the role of microalbuminuria, endothelial dysfunction (through flow-mediated dilatation [FMD] and soluble markers of vascular function), carotid intima-media thickness (CIMT), and increased blood pressure as risk factors for future CV[5–7] events.

However, serum uric acid has been seldom studied to date in studies investigating future risk for developing CV disease in preeclampsia despite it being characteristically high in this condition and despite its strong association with CV disease in nonpregnant subjects.[8] We therefore evaluated the role of uric acid in preeclamptic patients with a future history of metabolic and cardiorenal disease including blood pressure, microalbuminuria, endothelial function, CIMT, and uric acid in a case-control study design.

MATERIALS AND METHODS

Study Design and Participants

This is an observational case-control study that recruited patients with preeclampsia during their pregnancy and women whose pregnancies were not complicated by preeclampsia as control subjects. Case patients and control subjects were recruited from the Department of Obstetrics and Gynecology of Kayseri Education and Research Hospital, Turkey. The primary aim of this study was to investigate the effects of previous preeclampsia and uric acid on the future development of hypertension, kidney function, CIMT, and endothelial function. We included all available patients who had experienced a pregnancy complicated by preeclampsia from before January 2008. A total of 44 eligible patients with preeclampsia were initially examined in the study. Seven patients had a previous history of hypertension, 3 patients had chronic kidney disease, 8 patients were lost to follow-up, and 1 patient withdrew consent. Twenty-five patients with a history of preeclampsia were included in the final analysis.

Preeclampsia is diagnosed when blood pressure is 140 mm Hg systolic or greater or 90 mm Hg diastolic or greater on 2

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Conflict of interest: Dr. Johnson is an inventor on several patent and patent applications related to lowering uric acid in the treatment of metabolic and renal diseases that have been licensed to XORT Therapeutics. The other authors state that they have no proprietary interest in the products named in this article.

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separate readings taken at least 4 to 6 hours apart after 20 weeks gestation in an individual with previously normal blood pressure and proteinuria of 0.3 g (300 mg) or more of protein in a 24-hour urine sample.[9]

None of the preeclamptic women had had chronic hypertension and kidney disease as well as previous CV disease before the index pregnancy. The control subjects were randomly selected among women who had uncomplicated pregnancy during the same time period with women with previous preeclampsia. All baseline blood tests results were recorded at the time of delivery. The current evaluation was performed in May 2013. Follow-up period of both groups was similar (6.12 ± 3.59 years in the preeclampsia group vs 6.05 ± 4.06 years in the control group, $P = 0.32$).

After the study protocol was explained to them, the women who agreed to participate in the study were asked to visit our hospital for clinical and laboratory evaluation. All women with and without previous preeclampsia history underwent detailed clinical history and physical evaluation. A 24-hour ambulatory blood pressure measurement, CIMT, and FMD tests were also performed for all subjects. Physicians who performed the aforementioned tests were blinded to the status and group of the participants. Basic laboratory tests as well as clinical and demographic features of all participants during index pregnancy were recorded from patient charts. Diagnosis of hypertension was made on the basis of ambulatory blood pressure monitoring according to current guidelines.[10] The study was approved by the Kayseri Training and Research Hospital Ethics Committee and was conducted in accordance with the ethical principles set forth by the Declaration of Helsinki. All patients were included in the study after signing informed consent forms 5 years after pregnancy.

Flow-Mediated Dilatation Measurement

The determination of endothelial dysfunction was performed according to the study of Celermajer et al.[11] Measurements were made by a single observer who was blinded to the randomization status of the patients using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc, Bothell, WA) with a 12-MHz probe. All vasoactive medications were withheld for 24 hours before the procedure. After an overnight fast, the subjects remained at rest in the supine position for at least 15 minutes before the examination started. The subject's arm was comfortably immobilized in the extended position to allow consistent recording of the brachial artery 2 to 4 cm above the antecubital fossa. Three adjacent measurements of end-diastolic brachial artery diameter were made from single 2-dimensional frames. All of the ultrasound images were recorded on S-VHS videotape for a subsequent blinded analysis. A pneumatic tourniquet was inflated to 200 mm Hg with obliteration of the radial pulse. After 5 minutes, the cuff was deflated. Flow measurements were made 60 seconds after the deflation. The maximum FMD diameters were calculated as the averages of the 3 consecutive maximum-diameter measurements. The FMD was then calculated as the percentage of change in diameter compared with baseline resting diameters.

Carotid Intima-Media Thickness Measurement

The common carotid, the carotid bulb, as well as the near and far wall segments of the internal carotid were scanned bilaterally according to the consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force.[12] Before the examination, all subjects were at rest, lying in a supine position. The neck was positioned in hyperextension and slightly inclined at 45 degrees contralateral to the side of scanning to measure CIMT correctly. Images were obtained in longitudinal sections, with a single lateral angle of insonation, optimizing the image for the far wall. *Carotid intima-media thickness* was defined as the distance between the lumen-intima and the media-adventitia ultrasound interfaces. Measurements were performed off-line and consisted of 6 manual measurements at equal distances along 1 cm on the far wall of the common carotid. We considered the mean values in millimeters (mm) of left and right artery measurements for the analysis of the results.

Statistical Analysis

Data are expressed as mean ± SD, median, and interquartile range (IR) or as percentage frequency, as appropriate. Comparisons among the groups were made using the independent *t* test (normally distributed variables), Mann-Whitney test (nonnormally distributed variables), and χ^2 or Fischer test (categorical data). Among the patients, the comparisons were made using the paired *t* test. Correlations between the variables were investigated using the Pearson product-moment correlation coefficient, the Spearman rank correlation coefficient, or the point biserial correlation coefficient, as appropriate.

A P value of less than 0.05 was considered for statistical significance. All calculations were made using a standard statistical package (SPSS for Windows, version 19.0.1, Chicago, IL).

RESULTS

Forty-five women were studied, of which 25 had preeclampsia and 20 served as controls. None of the patients and controls had a history of hypertension before the index pregnancy. We

TABLE 1. Demographic, Clinical, and Biological Parameters Evaluated at the Time of Index Gestation

	Control group, n = 20	Preeclampsia group, n = 25	*P**
Age, y	27.25 ± 3.61	27.44 ± 6.68	0.90
No. pregnancies	2 (1–2)	1 (1–2)	0.14
Gestational age, wk	27.25 ± 3.61	27.44 ± 6.68	0.90
Diabetes, n (%)	0 (0)	1 (4)	1.00
Smoking, n (%)	0 (0)	3 (12)	0.24
BMI, kg/m^2	27.92 ± 2.69	29.14 ± 3.95	0.23
Creatinine, mg/dL	0.66 ± 0.15	0.67 ± 0.19	0.76
Uric acid, mg/dL	2.27 ± 0.38	4.36 ± 0.61	**<0.001**

Data are expressed as mean ± SD, percentages, or median with IR, as appropriate. Bold values are statistically significant.

*Comparison between the groups.

BMI indicates body mass index.

TABLE 2. Demographic, Clinical, and Biological Parameters at the Current Evaluation

	Control Group, n = 20	Preeclampsia Group, n = 25	*P**
Diabetes, n (%)	0 (0)	0 (0)	NA
Hypertension, n (%)	0 (0)	8 (32)	**0.001**
BMI, kg/m^2	28.55 ± 2.38	30.68 ± 4.38	**0.04**
Creatinine, mg/dL	0.69 ± 0.14	0.63 ± 0.14	0.21
Uric acid, mg/dL	4.09 ± 0.57	4.83 ± 1.21	**0.01**
Proteinuria, g/d	0.06 (0.03–0.08)	0.24 (0.18–0.32)	**<0.001**
Day SBP, mm Hg	125.85 ± 5.27	124.76 ± 15.45	0.74
Day DBP, mm Hg	78.35 ± 4.63	78.92 ± 12.79	0.84
Night SBP, mm Hg	116.75 ± 2.67	110.20 ± 16.98	0.07
Night DBP, mm Hg	65.45 ± 3.03	65.76 ± 13.78	0.91
Mean SBP, mm Hg	125.95 ± 2.82	121.24 ± 15.39	0.15
Mean DBP, mm Hg	74.70 ± 3.04	76.00 ± 12.52	0.62
FMD, %	14.35 (11.43–17.22)	9.64 (6.08–12.17)	**0.002**
CIMT, mm	0.52 ± 0.08	0.64 ± 0.12	**0.001**

Data are expressed as mean ± SD, percentages, or median with IR, as appropriate. Bold values are statistically significant.

*Comparison between the groups.

BMI indicates body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FMD, flow-mediated dilatation; NA, not applicable; SBP, systolic blood pressure.

examined these patients at 2 distinct time points: gestational and at 5 years after pregnancy.

Clinical and biological parameters evaluated at the first time point (during pregnancy) are presented in Table 1. There were no differences between the 2 groups in regard to age, number of previous pregnancies, gestational age, diabetes, smoking, body mass index (BMI), or serum creatinine. As expected, the women with preeclampsia were more likely to have higher serum acid uric levels (4.36 ± 0.61 vs 2.27 ± 0.38 mg/dL, $P < 0.001$).

Table 2 presents the clinical and biological characteristics evaluated at the second time point, which was at least 5 years after pregnancy. At this time, the patients who had preeclampsia were more likely to have hypertension and to have higher serum uric acid levels. In addition, the patients with preeclampsia had higher proteinuria and CIMT levels as well as lower FMD values than did the patients who did not have preeclampsia. The 2 groups were similar with regard to various ambulatory blood pressure monitoring parameters measured in the study (Table 2).

During the 5 years of follow-up, uric acid levels increased significantly only in the control group and this increase was significantly higher than that observed in the preeclampsia group (mean difference, 1.36 mg/dL; 95% confidence interval [CI], 0.69–2.02 mg/dL; $P < 0.001$; Fig. 1 and Table 3). The BMI was significantly higher at the second evaluation only in the preeclampsia group; however, compared with the control group, this difference did not reach statistical significance (mean difference, 0.92 kg/m^2; 95% CI, 3.91-2.07 kg/m^2; $P < 0.001$; Table 3). Serum creatinine levels did not change significantly in either of the 2 groups at the 2 evaluation points.

Table 4 shows the univariate associates of FMD and CIMT in the study population. Both parameters were correlated with preeclampsia and the current hypertension status. They also showed a moderate correlation with proteinuria and, more importantly, with gestational uric acid levels (coefficient of correlation of 0.40, $P = 0.01$ for FMD and coefficient of correlation of 0.37, $P = 0.01$ for CIMT, respectively). Owing to the limited number of patients, we did not perform a multivariable analysis to determine independent associates of FMD and CIMT.

DISCUSSION

Our study shows that CV disease risk factors are significantly more prevalent in patients with previous preeclampsia as compared with women without preeclampsia and also that the pathophysiological mechanisms associated with this disease, especially related to the vascular function and structure, persist long after the index event.

The relationship between preeclampsia and future development of CV disease is evident on the basis of large population studies.[13] The prevalence of CV risk factors increases after an episode of preeclampsia. In this regard, early-onset preeclampsia poses a greater risk for future CV disease. Several CV risk factors link the history of preeclampsia with the development of CV disease later in life. The most frequent of these factors are metabolic syndrome[14] and hypertension. Our results showed an increased prevalence of hypertension among the previously preeclamptic

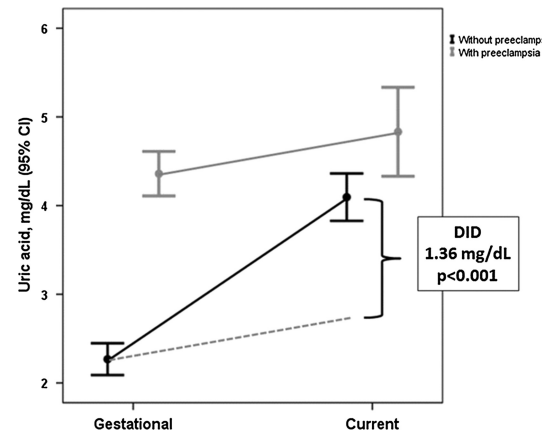

FIGURE 1. Evolution of uric acid levels between the 2 time evaluations in the 2 groups. DID indicates the difference in difference.

TABLE 3. Differences in BMI and Serum Creatinine Levels Between the 2 Study Time Points in Each Group

	Control Group, n = 20		Preeclampsia Group, n = 25		Difference in Difference (Control-Group 2)	
	Mean Difference (95% CI)	*P*	Mean Difference (95% CI)	*P*	Mean Difference (95% CI)	*P*
BMI, kg/m^2	0.63 (–0.42 to 1.67)	0.23	1.5 (0.30–2.79)	**0.02**	−0.92 (–3.91 to 2.07)	0.54
Creatinine, mg/dL	0.03 (–0.08 to 0.14)	0.57	−0.04 (–0.14 to 0.07)	0.44	−0.07 (–0.21 to 0.07)	0.31

Bold values are statistically significant.

*Comparison between the groups.

BMI indicates body mass index; CI, confidence interval.

women compared with the controls. However, of note, ambulatory blood pressure measurements were comparable in both groups, suggesting adequate blood pressure control in the patient group.

It is an intriguing question why an acute obstetrical complication that was virtually cured by delivery is strongly related to the development of CV disease many years after the index event. Several studies tried to explain this link, suggesting an increased frequency of established CV risk factors such as metabolic syndrome, hypertension, and insulin resistance.[15]

Pathophysiology of preeclampsia involves widespread endothelial dysfunction.[16] Thus, it is plausible to think that an increased future risk for CV disease in women with previous preeclampsia may arise at least in part from persistence of endothelial dysfunction. To test this hypothesis, Yinon et al.[17] evaluated vascular health of women with early-onset preeclampsia, late-onset preeclampsia, and intrauterine growth restriction without preeclampsia, along with women with no history of preeclampsia. The study revealed that only women with early-onset preeclampsia and women with intrauterine growth restriction without preeclampsia showed impaired vascular function (assessed through FMD, flow-independent vasodilatation, and arterial stiffness). However, this study had small sample sizes for each subgroup and the follow-up duration was up to 24 months postpartum.

To overcome the limitations of the aforementioned study, recently, Sandvik et al.[18] conducted a case-control study in which they examined women with and without a preeclampsia history 10 years before study inclusion. The authors found that preeclampsia was not associated with impaired FMD or increased CIMT, 10 years after pregnancy, in previously healthy women. On the other hand, a history of preeclampsia was associated with significant changes in circulating factors that might represent subtle endothelial dysfunction, such as higher levels of uric acid and soluble fms-like tyrosine kinase as well as lower levels of HDL cholesterol. The conflicting results of these reported studies[17–19] may be caused by the severity of the experienced preeclampsia, heterogeneity, and small sample size of the included patients in addition to selection bias. In the absence of sufficiently powered prospective studies, this question seems to be left unanswered.

Recent studies showed that elevated levels of serum uric acid can stimulate oxidative stress and endothelial dysfunction.[8,20] However, uric acid has been shown not to be a consistent predictive factor for the development of preeclampsia,[21] whereas its levels generally increase once the disease occurs, and they correlate with disease severity.[22] Furthermore, little is known whether elevated serum uric acid is a factor that conveys increased future CV disease risk. Our results were also in accordance with some previous reports.[13] Moreover, this difference was independent of creatinine clearance levels of the groups. Preeclamptic women had higher serum uric acid levels both at the time of the gestation and evaluation 10 years later. Thus, serum uric acid may be one of the missing factors that could be related to the persistence of impaired endothelial function after recovery of preeclampsia.

Microalbuminuria is now accepted as an independent CV disease risk factor in patients with diabetes mellitus and hypertension as well as in the general population.[23] It is also a diagnostic criterion for the diagnosis of preeclampsia. Most preeclamptic women with overt proteinuria recover completely after 3 months of delivery. However, some women, especially those with early onset and severe preeclampsia, continue to have microalbuminuria many years after the preeclamptic episode. A meta-analysis involving 273 patients with preeclampsia and 333 patients with uncomplicated pregnancies showed that 31% of women with a history of preeclampsia had microalbuminuria compared with 7% of women with uncomplicated pregnancies. There was a 4-fold increased risk for a mean of 7 years of postpartum follow-up.[24] However, in a recent study of otherwise healthy women, preeclampsia 10 years earlier was not associated with an increased risk for persistent microalbuminuria.[25] In contrast to this latter study, in our study, women with previous preeclampsia had significantly higher microalbuminuria level compared with women with uncomplicated pregnancies. Much larger samples are needed to determine the role of prior history of preeclampsia as a risk factor for persistent microalbuminuria later in life.

TABLE 4. Univariate Associates of FMD and CIMT

	FMD		CIMT	
	Correlation Coefficient	*P*	Correlation Coefficient	*P*
Current hypertension (0 indicates no; 1, yes.)	0.37	0.01	−0.37	0.01
Group (1 indicates without preeclampsia; 2, with preeclampsia.)	−0.42	0.004	0.49	0.001
Proteinuria, g/d	−0.33	0.03	0.33	0.03
Gestational uric acid, mg/dL	−0.40	0.01	0.37	0.01
CIMT, mm	−0.38	0.01	NA	
FMD, %	NA		−0.38	0.01

CIMT indicates carotid intima-media thickness; FMD, flow-mediated dilatation; NA, not applicable.

As a marker of generalized atherosclerosis, CIMT has been studied in preeclamptic women during gestation and, thereafter, in several studies. Whereas some studies showed increased CIMT in pregnancies complicated with preeclampsia compared with uncomplicated pregnancies,[26] others found no such difference.[27] A few studies also looked at whether increased CIMT is present later in life in women with a past preeclamptic episode, with conflicting results.[18] Our results showed that CIMT was significantly greater in women with previous preeclampsia compared with controls.

Some limitations of our study deserve mention. First, this is not a prospective randomized study; thus, causality cannot be determined. Second, the sample size in our study is relatively small to detect subtle differences. Thus, we could not perform multivariate analysis owing to overfitting of the model or different subgroup analyses. Third, we did not have any information about the birth weights of children and, as such, we were not able to define our population from this point of view. On the other hand, the current study has also some strengths. First, our observation period is fairly long, which is suitable to evaluate remote effects of a preeclamptic episode. Second, we evaluated a panel of CV risk factors including endothelial dysfunction, microalbuminuria, blood pressure, and CIMT; as such, we could take a better overall picture of the CV health status of the subjects.

In conclusion, in this observational case-control study, we found increased CV disease risk markers among women with a history of preeclampsia as compared with women with uncomplicated pregnancies. The women with previous preeclampsia had worse endothelial function, more atherosclerosis, higher microalbuminuria, and higher serum uric acid levels compared with the controls. Thus, uric acid and microalbuminuria might be likely conveyors of increased future CV risk in preeclamptic women. Obviously, larger studies with prospective design are required to settle down the contradictions observed in the literature.

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