Longitudinal Change in Arterial Stiffness After Delivery in Women With Preeclampsia and Normotension: a Prospective Cohort Study

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Research article

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Abstract

BACKGROUND: Preeclampsia is associated with increased arterial stiffness during pregnancy. However, data on the longitudinal change in arterial stiffness after delivery in women with preeclampsia are lacking. We aimed to examine the longitudinal change in arterial stiffness after delivery in women with preeclamptic and normotensive pregnancies, using the cardio-ankle vascular index for assessment of arterial stiffness.

METHODS: Pregnant women with preeclampsia (n=37) and normotension (n=36) who gave birth at Seoul National University Bundang Hospital between March 2013, and May 2016, were enrolled and followed up at day 1, 6 months, and 12 months after delivery. The longitudinal change in the cardio-ankle vascular index and other variables including blood pressure, lipid profiles, serum creatinine, liver enzymes were compared between the two groups using mixed-effect model, and interactions among the main predictors were examined.

RESULTS: The longitudinal change in the cardio-ankle vascular index did not significantly differ between the two groups (β=0.11, 95% CI: -0.31 – 0.54, p=0.60). Predictors of the longitudinal change in the cardio-ankle vascular index included age, time since delivery, body mass index, and diabetes mellitus. Women with preeclampsia showed significantly elevated blood pressure, lipid profiles, serum creatinine, and liver enzymes compared to women with normotension over the course of one year of follow up.

CONCLUSION: Preeclampsia is associated with unfavorable blood pressure and metabolic indices after delivery. However, there was no difference in the longitudinal change in arterial stiffness between women with preeclampsia and normotension over the course of one year after delivery.

Introduction

Hypertensive pregnancy disorders, such as preeclampsia or eclampsia, are one of the leading causes of maternal mortality during pregnancy and the puerperium, affecting 2–8% of gestations.[1–3] They are associated with vascular endothelium dysfunction, insulin resistance, hyperlipidemia, hypercoagulability, and inflammation.[4–6] Thus, hypertensive pregnancy disorders share many etiologies with cardiovascular disease. There is accumulating evidence that women with a history of hypertensive pregnancy disorders have increased risks of cardiovascular disease.[7, 8]

Arterial stiffening develops from a complex interaction between stable and dynamic changes in the structural and cellular elements of the vessel wall,[9] and it is a marker for increased cardiovascular risks, including myocardial infarction, heart failure, and total mortality.[10] Previous studies suggest that women with preeclampsia have increased arterial stiffness during pregnancy compared to pregnant women with normotension.[11, 12] However, there are few reports on the longitudinal change in arterial stiffness after delivery in women with preeclampsia.

In the present study, we aimed to longitudinally follow arterial stiffness, as assessed by the cardio-ankle vascular index (CAVI), blood pressure (BP) and other metabolic indices for one year after delivery, and to investigate the predictive markers of increased postpartum arterial stiffness.

Materials And Methods

Study Participants

This prospective cohort study included 37 women with preeclampsia and 36 women with normotension who gave birth to a child at SNUBH between March 2013 and May 2016. SNUBH is a teaching and tertiary referral hospital that provides care for high-risk deliveries. Women aged 18 to 45 years old were eligible for the study. Women with a pregnancy that ended in stillbirth, and those who were hemodynamically compromised or had peripartum bleeding complications were excluded from the study.

The diagnosis of preeclampsia was made based on the criteria of the International Society for the Study of Hypertension in Pregnancy.[13] Under this classification, preeclampsia was defined as diastolic BP of at least 110 mmHg on one occasion or diastolic BP of at least 90 mmHg on two consecutive occasions more than four hours apart, in combination with proteinuria (≥ 300 mg total protein in a 24-hour urine collection or, if this was not available, ≥ 2 + proteinuria by dipstick analysis on two consecutive occasions at least four hours apart) that developed after 20 weeks of gestation in women who were previously normotensive.

Study participants were treated at the physician's discretion according to current recommendations and guidelines for the peripartum and postpartum periods.

Study protocol

The cardio-ankle vascular index (CAVI), which is calculated based on the stiffness parameter, is theoretically independent of changes in BP. Because of this distinct advantage, the CAVI has been applied clinically to assess arterial stiffness in patients with known cardiovascular diseases (atherosclerosis, coronary heart disease, and stroke), as well as in those at risk for cardiovascular diseases, such as patients with hypertension, diabetes, obesity, and advanced age.[14–16]

The CAVI was measured on day 1, 6 months, and 12 months after delivery in both study groups.

The body mass index (BMI), BP, lipid profiles, serum creatinine, aspartate transaminase (AST), and alanine transaminase (ALT) levels were assessed simultaneously with the CAVI.

Laboratory Measurements

Blood samples were collected from the antecubital vein after 8–10 hours of fasting. Laboratory performance was monitored regularly by a quality control program. Hemoglobin was measured using the XE-2100 D (Sysmex Inc., Kobe, Japan). Serum creatinine, ALT, AST, total cholesterol, high-density

lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels were measured using the Beckman Coulter AU 5800 analyzer (Beckman Coulter Inc., Brea, CA, USA).

Measurement of BP and the CAVI

BP was measured three times on the right arm, using an appropriately sized arm cuff and validated upper arm BP monitor (HEM-7200; Omron healthcare Co., Kyoto, Japan), after the study participant had rested in a seated position for at least 5 minutes.[17] The final BP value was obtained by averaging the second and third measurements. Height and body weight were measured during each visit using standardized equipment (G-310c, G-Tech Co., Uijeongbu, South Korea).

The CAVI was measured using a Vasera VS-1000 vascular screening system (Fukuda Denchi, Tokyo, Japan), with the participant resting in a supine position. The principles of the CAVI have been described in previous reports.[16, 18] The automatically obtained data were analyzed using VSS-10 software, and the right and left CAVIs were calculated. The average value of the right and left CAVIs was used for analysis.

Statistical Analysis

Data distributions were examined and checked for potential outliers. Descriptive statistics were used to summarize the baseline demographic and clinical characteristics of the study participants. Group differences were evaluated using the t-test or Wilcoxon test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables.

The relationship between the presence of preeclampsia and longitudinal changes in the CAVI, with and without control for other potential covariates, was examined using a mixed-effects model to adjust for repeated measurements within participants. As the mixed-effects model accounted for all available data points, respondents with incomplete datasets were not excluded from analysis (under the assumption that missing data occurred at random). Interactions among the main predictors in the final model were examined. Group differences were also evaluated across the reporting time points for several other physiological parameters of interest using mixed-effects modeling. All reported p-values are 2-tailed, and $\alpha = 0.05$ was set as the threshold for statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Systemic arterial stiffness undergoes major changes during pregnancy. Previous longitudinal studies of women with normotensive pregnancies have demonstrated that the pulse wave velocity (PWV), an index of arterial stiffness, decreases during the second trimester, increases during the third trimester and delivery, and then decreases during the first month postpartum.[19] Another study that longitudinally followed the changes in PWV throughout pregnancy and 1 month after delivery in women with normal pregnancies showed a similar pattern of change in the PWV.[20] On the other hand, in patients with pregnancy-induced hypertension, the PWV did not decrease between the first and second trimesters, and markedly increased after delivery.[19, 21],[22] The key finding that is consistent in the present and previous

studies is an increased postpartum arterial stiffness parameter from 7 weeks up to 2–3 years postpartum.[23] The present study showed an elevated CAVI up to 6 months postpartum. The timing and persistence of endothelial dysfunction after delivery in women with a history of preeclampsia is not fully elucidated. To our knowledge, this study is the first longitudinal report of arterial stiffness using the CAVI, and the results further indicate that there are measurable changes in the maternal vasculature that arise during pregnancy.

Preeclampsia is associated with greater and more prolonged postpartum increases in arterial stiffness.[20] However, few studies have compared the postpartum longitudinal change in arterial stiffness between women with preeclamptic and normotensive pregnancies. Most studies utilized a cross-sectional design, with arterial stiffness mainly estimated by pulse wave analysis (PWA).[11, 24] BP is one of the most important contributing factors to the PWA,[25] and unfavorable arterial stiffness indices in women with a history of preeclampsia may be attributable to a higher incidence of hypertension. Thus, in the present study, we examined the longitudinal change in arterial stiffness for one year after delivery using the CAVI, which is less affected by BP than is the PWA. We observed a significant group difference in the mean CAVI at 6 months after delivery; however, at 12 months, the group difference was no longer significant. Furthermore, the overall difference between the groups in the longitudinal change in the mean CAVI over the course of one year after delivery failed to reach statistical significance. This result may suggest that postpartum changes in arterial stiffness in women with preeclampsia are reversible, as is the case for normotensive pregnancies; however, the recovery may be slower in women with preeclampsia.

Clinical Implications

In the present study, we confirmed that preeclamptic pregnancy is associated with higher postpartum trajectories of age- and time-adjusted BP and metabolic indices, such as total and LDL cholesterol, creatinine, and AST/ALT, than normotensive pregnancy, which is consistent with previous reports from Western countries.[26, 27] These factors may contribute to the development of long-term cardiovascular disease. Thus, the present results suggest that an unfavorable cardiovascular risk profile may contribute to the development of future cardiovascular disease to a greater extent than does endothelial damage caused by preeclampsia persisting beyond the postpartum recovery period.

Diabetes mellitus was independently associated with an increased CAVI in the mixed-effect model. Gestational diabetes is associated with cardiovascular disease later in life, and the present results suggest that increased arterial stiffness may play a role. Women with gestational diabetes should be closely followed up, even if they do not have a history of preeclampsia.

Research Implications

The study results suggest that a meticulous follow-up and strict control of cardiovascular disease risk factors in women with a history of preeclampsia is needed. However, to date, there is limited research

evaluating the efficacy of different interventional approaches addressing postpartum cardiovascular health in women with a history of preeclampsia.

Strengths and Limitations

To the best of our knowledge, we have performed the longest follow-up study of postpartum arterial stiffness. In addition, this is the first study that compared the longitudinal change in the CAVI between postpartum women with preeclamptic and normotensive pregnancies.

The present study has several limitations. First, the sample size was relatively small. Second, only 76.7% and 61.6% of women completed the study assessments at 6 and 12 months, respectively. Participants who dropped-out were too busy with childcare to participate in the study. In South Korea, the burden of infant care is usually concentrated on mothers, and support from the welfare system is inadequate.[28] Thus, the assumption that data was missing at random is reasonable, and the use of mixed-effects modeling under this assumption is appropriate. Third, we only used the CAVI to assess arterial stiffness. Other indices, such as the PWV or augmentation index, were not evaluated. However, the efficacy of the CAVI has been validated in numerous clinical conditions, and is correlated with other arterial stiffness markers.[14, 15, 18]

Discussion

Principal Findings

The observation of a difference between the groups at 6 months, with a higher mean CAVI in the pre-eclampsia group, appeared to be related to the older age of women and their diabetic status in the preeclamptic group, as the group difference was resolved with adjustment. However, by one year, there was no statistically significant difference in the CAVI between the groups. Both groups showed a statistically significant decline in the CAVI by 6 months, with no subsequent meaningful change, and there was no suggestion that this improvement was dependent on other factors.

Thus, although women with preeclamptic pregnancies persistently showed worse cardiovascular risk profile trajectories after delivery than did women with normotensive pregnancies, the arterial stiffness trajectory over the course of one year after delivery did not differ between women with preeclampsia and normotension.

Conclusion

During one year of postpartum follow up, women with preeclampsia showed a more unfavorable cardiovascular risk profile trajectory than pregnant women with normotension. However, there was no significant longitudinal difference in arterial stiffness between women with preeclampsia and normotension. Both groups did, however, experience a decrease in arterial stiffness, which appeared to

change little after 6 months postpartum. Our findings suggest that a meticulous follow-up and strict control of cardiovascular disease risk factors in women with a history of preeclampsia is advisable.

Abbreviations

AST, aspartate transaminase; ALT, alanine transaminase; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; PWA, pulse wave analysis; PWV, pulse wave velocity; SNUBH, Seoul National University Bundang Hospital; IRB, institutional review board

Declarations

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Authors' Contributions

Sehun KIM : Writing – original draft, Investigation, Visualization.; Hyun Ja LIM : Methodology, Formal Analysis, Data curation.; Jeung-Ran KIM : Investigation.; Kung Joon OH : Methodology, Supervision, Validation, Writing – Reviewing & Editing.; Joon-Seok HONG : Conceptualization, Supervision, Validation, Writing – Reviewing & Editing.; Jung-Won SUH : Conceptualization, Methodology, Project administration, Writing – Reviewing & Editing. All authors have read and approved the manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (SNUBH), South Korea (IRB No. B-1402-240-006). Written informed consent was obtained from all participants before enrolment.

Competing interests

The authors declare no conflict of interest.

Trial registration

www.clinicaltrials.gov, NCT04142268. Registered 29 October 2019 – Retrospectively registered, https://www.clinicaltrials.gov/ct2/results?cond=&term=NCT04142268&cntry=&state=&city=&dist=

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Tables

Table 1. Baseline demographic and clinical characteristics

Preeclampsia (n=37)	Control (n=36)	P value[#]	
Age, years	34.8 ± 3.6	32.9 ± 3.6	0.029
History of preeclampsia, n (%)	2 (5.4)	1 (2.8)	0.999
Peak body weight during pregnancy, kg	70.4 ± 11.8	65.6 ± 7.5	0.042 (0.108*)
Primipara	24 (64.9)	24 (66.7)	0.871
Twins, n (%)	4 (10.8)	1 (2.8)	0.358
Gestational week at delivery	33.7 ± 3.0	37.7 ± 2.0	<0.001
Fetal birth weight, kg	1.79 ± 0.58	2.93 ± 0.52	<0.001
Waist-to-hip ratio	0.92 ± 0.05	0.92 ± 0.06	0.874
BMI, m^2/kg	27.4 ± 5.0	25.0 ± 2.8	0.015(0.050*)
Mean CAVI [$]	6.92 ± 1.69	6.53 ± 1.50	0.306(0.032*)
Hypertension[†], n (%)	2(5.4)	0	0.494
Diabetes mellitus[‡], n (%)	4(10.8)	0	0.115
SBP, mmHg	142.4 ± 12.7	111.4 ± 10.5	< 0.001
DBP, mmHg	83.9 ± 9.3	63.2 ± 7.8	< 0.001
Hemoglobin, mg/dL	12.0 ± 2.0	11.4 ± 1.8	0.164
Total cholesterol, mg/dL	232.6 ± 49.6	208.6 ± 46.3	0.036
HDL cholesterol, mg/dL	59.9 ± 14.6	62.6 ± 13.1	0.419
LDL cholesterol, mg/dL	126.2 ± 33.0	112.2± 33.7	0.082 (0.017*)
Triglyceride, mg/dL	255.6 ± 92.5	213.6 ± 60.5	0.026 (0.061*)
Creatinine, mg/dL	0.693 ± 0.255	0.532 ± 0.092	0.001 (0.007*)
AST, IU/L	31.0 ± 17.2	17.9 ± 7.6	< 0.001
ALT, IU/L	27.0 ± 26.9	11.4 ± 6.2	0.002(< 0.001*)
Hypertension treatment, n (%)	23 (62.2%)	0%	< 0.001
Treatment regimen, n (%)			
Single drug	13 (56.5)		
Two drugs	8 (34.8)		
Three drugs	2 (8.7)		

Type of antihypertensive drug, n (%)	
CCB	23 (100%)
BB	2 (8.7%)

Data are presented as numbers and percentages or mean ± SD. [#]T-test or Chi-square test. *The Mann-Whitney test was used due to a skewed distribution. [$]The mean CAVI is the average of the right and left CAVIs. [†]refers to pre-pregnancy hypertension. [‡]Two women had type-1 diabetes mellitus; the remaining women had type-2 diabetes mellitus.

SD, Standard deviation; BMI, body mass index; CAVI, cardio-ankle vascular index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CCB, calcium channel blocker; BB, beta blocker

Table 2A. Between-subject (group) differences in the mean CAVI[$] at each time point

	Time	Control	Preeclampsia	p-value
Mean CAVI	Day 1	6.53 (5.98, 7.08)	6.92 (6.39, 7.45)	0.31
	6 months	6.23 (5.95 ,6.51)	6.63 (6.40, 6.87)	0.03
	12 months	6.59 (6.28, 6.89)	6.20 (5.87, 6.53)	0.09

Data are presented as mean and 95% C.I. [$]The mean CAVI is the average of the right and left CAVIs.

CAVI, cardio-ankle vascular index; C.I, confidence interval

Table 2B. Within-subject (time) differences in the mean CAVI[$], with comparisons between pairs of time points

	Group	Day 1	6 months	12 months	p-value
Mean CAVI	Control	6.52 (6.15, 6.91)	6.23 (5.74, 6.72)	-	0.61
		6.52 (6.15, 6.91)	-	6.59 (6.08, 7.09)	0.98
			6.23 (5.74, 6.72)	6.59 (6.08.7.09)	0.57
	Preeclampsia	6.92 (6.51, 7.33)	6.64 (6.15, 7.12)	-	0.64
		6.92 (6.51, 7.33)	-	6.20 (5.57, 6.83)	0.14
		-	6.64 (6.15, 7.12)	6.20 (5.57, 6.83)	0.52

Data are presented as mean and 95% C.I. [$]The mean CAVI is the average of the right and left CAVIs.

CAVI, cardio-ankle vascular index; C.I, confidence interval

Table 3. Predictors of the longitudinal change in the mean CAVI[$] from mixed-effects modeling

	β estimate ± SE	95% C.I	p-value
Time since delivery:	-	-	0.015
Day 1	-0.54 ± 0.22	-0.97, -0.11	0.012
6 months	-0.62 ± 0.24	-1.10, -0.14	
12 months			
Group:	-	-	0.600
Control	0.11 ± 0.21	-0.31, 0.54	
Preeclampsia			
BMI	-0.07 ± 0.02	-0.12, 0.03	0.003
Age	0.08 ± 0.03	0.02, 0.14	0.013
Diabetes Mellitus:	-	-	0.012
No	1.07 ± 0.41	0.25, 1.89	
Yes			

[$]The mean CAVI is the average of the right and left CAVIs. Interactions between covariates in the final model were examined and none were found to be statistically significant.

SE, standard error; C.I, confidence interval; BMI, body mass index

Table 4. Impact of preeclampsia on age- and time-adjusted longitudinal changes in blood pressure and metabolic indices

		β estimate	95% CI	p-value
Systolic BP, mmHg	Control	-		
	Preeclampsia	21.64	15.86 – 27.42	<0.0001
Diastolic BP, mmHg	Control	-		
	Preeclampsia	16.09	11.95 – 20.23	<0.0001
Waist/Hip ratio	Control	-		
	Preeclampsia	0.03	-0.11 – 0.11	0.960
Total cholesterol, mg/dL	Control	-		
	Preeclampsia	20.45	2.04 – 38.86	0.030
LDL cholesterol, mg/dL	Control	-		
	Preeclampsia	14.12	1.17 – 27.06	0.033
TG, mg/dL	Control	-		
	Preeclampsia	31.67	0.34 – 63.00	0.048
HDL cholesterol, mg/dL	Control	-		
	Preeclampsia	-1.80	-7.26 – 3.65	0.512
Creatinine, mg/dL	Control	-		
	Preeclampsia	0.115	0.032 – 0.197	<0.0001
AST, IU/L	Control	-		
	Preeclampsia	4.78	1.22 – 8.34	0.009
ALT, IU/L	Control	-		
	Preeclampsia	7.23	1.51 – 12.96	0.014

Mixed-effects modeling was used to adjust for repeated measurements within participants.

C.I, confidence interval; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; AST, aspartate transaminase; ALT, alanine aminotransferase

Figures

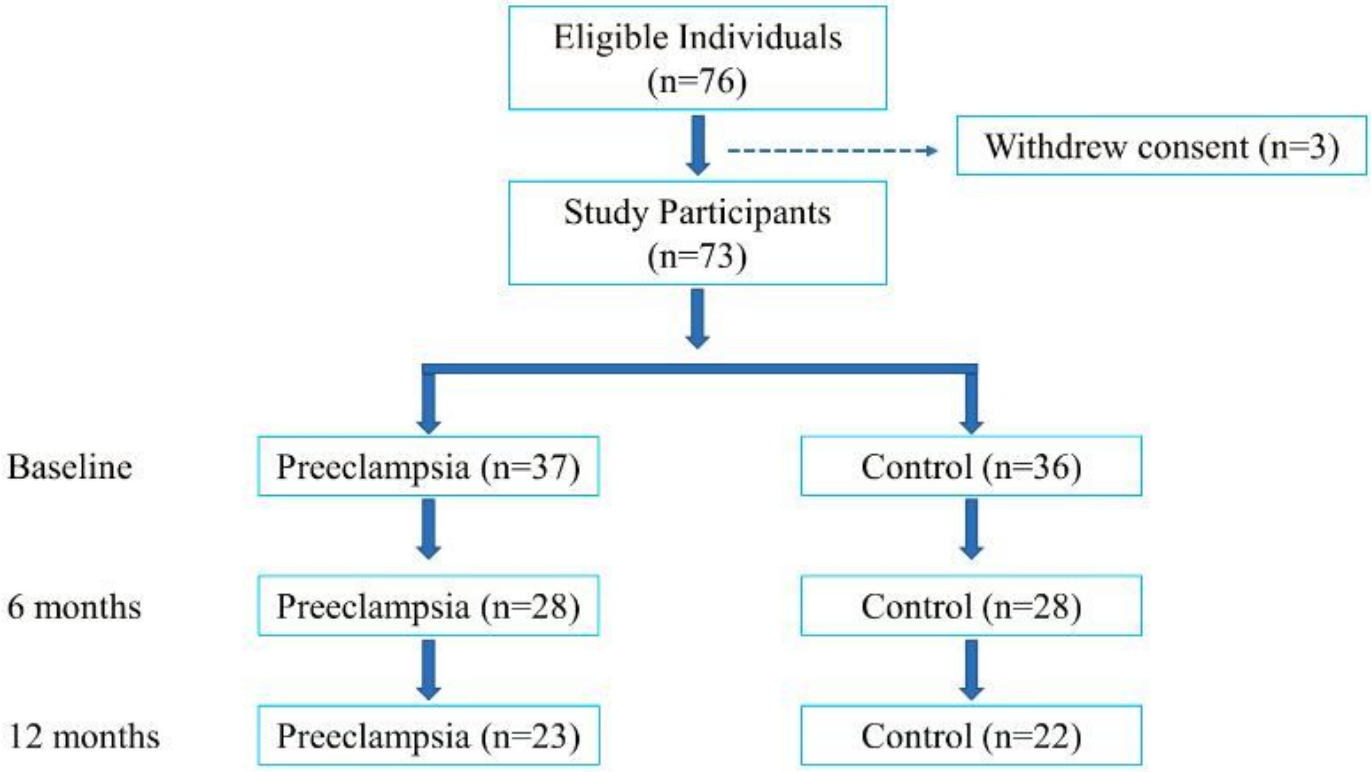

Figure 1

Study Flow Chart

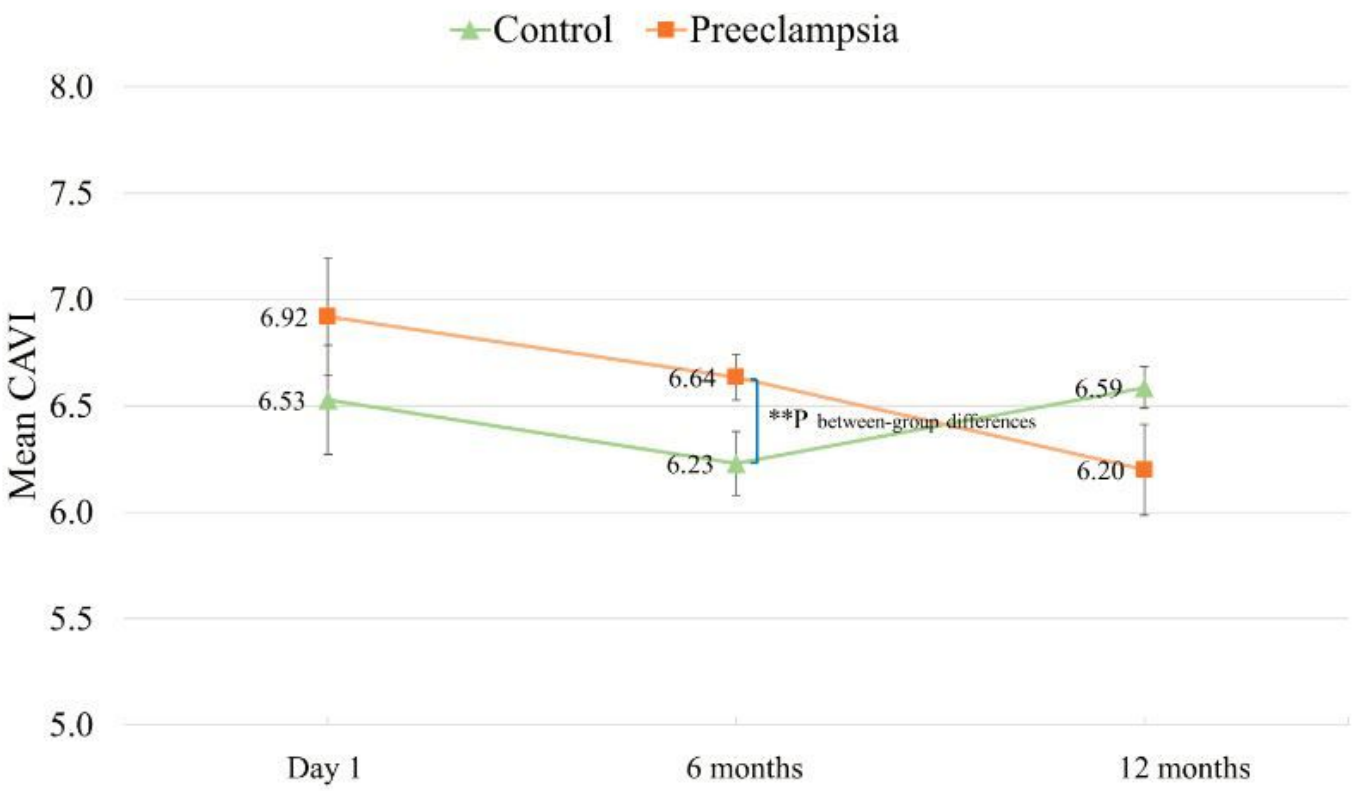

Figure 2

Mean CAVI over time according to group from unadjusted mixed modeling Data are presented as the mean level ± SE, and significant differences are indicated by double asterisks (** $p<0.05$). CAVI, cardio-ankle vascular index; SE, standard error