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Original article

Evaluation of homocysteine and asymmetric dimethyl arginine (adma)levels in hypertensive disorders of pregnancy

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Abstract

Background: *Hypertensive disorders of pregnancy (HDP) are prevalent complications, contributing significantly to maternal and perinatal morbidity. Elevated levels of homocysteine and asymmetric dimethylarginine (ADMA) may be linked to the severity of these conditions.*

Method: *This study evaluated homocysteine and ADMA levels in 210 pregnant women, including 110 with HDP and 100 normotensive controls. Blood samples were collected, and biomarker levels were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed to compare levels between groups and assess correlations with hypertension severity.*

Results: *The hypertensive group showed significantly higher mean homocysteine (14.3 ± 3.5 µmol/L) and ADMA (0.78 ± 0.21 µmol/L) levels compared to controls (8.7 ± 2.1 µmol/L and 0.49 ± 0.18 µmol/L, respectively; $p < 0.001$). Among subgroups, mean homocysteine levels trended upward from gestational hypertension to eclampsia, but without statistical significance ($p = 0.075$). The incidence of adverse pregnancy outcomes, including preterm birth and low birth weight, was significantly higher in the hypertensive group.*

Conclusion: *Elevated homocysteine and ADMA levels are associated with the severity of HDP, suggesting their potential as biomarkers for risk assessment and management in pregnant women.*

Keywords: *Hypertensive disorders; homocysteine; asymmetric dimethylarginine; pregnancy; biomarkers.*

Introduction:

Hypertensive disorders of pregnancy (HDP) are among the most common complications during pregnancy and a leading cause of maternal and perinatal morbidity and mortality worldwide. These disorders encompass a spectrum of conditions, including gestational hypertension, preeclampsia, and eclampsia, which affect approximately 5-10% of pregnancies. The pathophysiology of HDP is multifactorial and not fully understood, but endothelial dysfunction, impaired placental development, and altered vascular responses are recognized as key contributors.[1] Emerging evidence suggests that elevated levels of homocysteine and asymmetric dimethylarginine (ADMA) may play a significant role in the development and progression of HDP. [2]

Homocysteine, a sulfur-containing amino acid, is linked to vascular dysfunction and is considered an independent risk factor for cardiovascular diseases. Increased homocysteine levels in pregnancy have been associated with endothelial damage and oxidative stress, contributing to the development of hypertension and preeclampsia.[3] Similarly, ADMA, an endogenous inhibitor of nitric oxide synthase, is a key regulator of nitric oxide (NO) production and vascular homeostasis. Elevated ADMA levels reduce NO bioavailability, leading to endothelial dysfunction, vasoconstriction, and increased vascular resistance—factors that are closely related to the pathogenesis of hypertensive disorders in pregnancy.[4]

Given the potential involvement of homocysteine and ADMA in HDP, evaluating their levels in pregnant women with hypertensive disorders may provide valuable insights into the mechanisms underlying these conditions and help identify

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potential biomarkers for early detection and management. [5]

This study aims to assess the levels of homocysteine and ADMA in hypertensive disorders of pregnancy, exploring their association with the severity of the condition and their potential as predictive markers for adverse maternal and fetal outcomes.

Method:

This study was conducted to evaluate the levels of homocysteine and asymmetric dimethylarginine (ADMA) in patients with hypertensive disorders of pregnancy. A total of 210 pregnant women were enrolled, comprising 110 women diagnosed with hypertension and 100 normotensive women who served as the control group. The hypertensive group included individuals with gestational hypertension, preeclampsia, and eclampsia. Participants were recruited from the Obstetrics and Gynecology department of the hospital.

Venous blood samples were collected from all participants after obtaining informed consent. Serum levels of homocysteine and ADMA were measured using the enzyme-linked immunosorbent assay (ELISA) method, following the manufacturer's protocols. The ELISA kits used were highly sensitive, ensuring accurate quantification of both biomarkers. All samples were processed in the hospital's central laboratory, and each assay was performed in duplicate to minimize errors and ensure the reliability of results.

Data on demographic characteristics, clinical history, and pregnancy outcomes were collected from the medical records of the participants. Statistical analysis was performed to compare the homocysteine and ADMA levels between the hypertensive and control groups, and the association of these biomarkers with the severity of hypertensive disorders was evaluated. The results were presented as mean ± standard deviation, and a p-value of <0.05 was considered statistically significant.

Table 1: Demographic Characteristics of Study Participants

Characteristic	Hypertensive Group (n=110)	Control Group (n=100)	p-value
Age (years)	29.5 ± 5.4	28.3 ± 5.1	0.100
Gestational Age (weeks)	34.1 ± 2.9	35.2 ± 3.0	0.007*
Primigravida (%)	58 (52.7%)	52 (52%)	0.916
BMI (kg/m²)	28.9 ± 4.	27.4 ± 3.9	0.007*

The demographic characteristics of the study participants are summarized in Table 1. The mean age of participants in the hypertensive group was 29.5 ± 5.4 years, compared to 28.3 ± 5.1 years in the control group, with no significant difference between the two groups (p = 0.100). The mean gestational age was significantly lower in the hypertensive group (34.1 ± 2.9 weeks) than in the control group (35.2 ± 3.0 weeks), with a p-value of 0.007. The proportion of primigravida participants was similar between the hypertensive group (52.7%) and the control group (52%), with no significant difference (p = 0.916). Additionally, the mean body mass index (BMI) was significantly higher in the hypertensive group (28.9 ± 4.0 kg/m²) compared to the control group (27.4 ± 3.9 kg/m²), with a p-value of 0.007, indicating a notable difference in BMI between the two groups.

Table 2: Comparison of Homocysteine and ADMA Levels Between Groups

Biomarker	Hypertensive Group (n=110)	Control Group (n=100)	p-value
Homocysteine (µmol/L)	14.3 ± 3.5	8.7 ± 2.1	< 0.001*
ADMA (µmol/L)	0.78 ± 0.21	0.49 ± 0.18	< 0.001*

Table 2 presents the comparison of homocysteine and ADMA levels between the hypertensive and control groups. The mean homocysteine level in the hypertensive group was significantly higher at 14.3 ± 3.5 µmol/L compared to 8.7 ± 2.1 µmol/L in the control group, with a p-value of < 0.001, indicating a highly significant difference. Similarly, the mean ADMA level was elevated in the hypertensive group (0.78 ± 0.21 µmol/L) compared to the control group (0.49 ± 0.18 µmol/L), with a p-value of < 0.001, further showing a statistically significant difference between the two groups for both biomarkers.

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Table 3: Homocysteine and ADMA Levels by Type of Hypertensive Disorder

Group	Homocysteine (µmol/L)	ADMA (µmol/L)
Gestational Hypertension (n=97)	13.2 ± 3.1	0.72 ± 0.19
Preeclampsia (n=8)	14.8 ± 3.4	0.81 ± 0.22
Eclampsia (n=5)	16.1 ± 4.2	0.89 ± 0.24
P value	0.075	0.101

Table 3 compares the homocysteine and ADMA levels based on the type of hypertensive disorder. The mean homocysteine levels were 13.2 ± 3.1 µmol/L in the gestational hypertension group, 14.8 ± 3.4 µmol/L in the preeclampsia group, and 16.1 ± 4.2 µmol/L in the eclampsia group. Although there is an increasing trend in homocysteine levels from gestational hypertension to eclampsia, the difference was not statistically significant (p = 0.075).

Similarly, the mean ADMA levels showed a gradual increase across the groups, with 0.72 ± 0.19 µmol/L in the gestational hypertension group, 0.81 ± 0.22 µmol/L in the preeclampsia group, and 0.89 ± 0.24 µmol/L in the eclampsia group. However, this difference in ADMA levels was also not statistically significant (p = 0.101).

Table 4: Correlation Between Homocysteine, ADMA, and Severity of Hypertension

Biomarker	Mild Hypertension (n=60)	Severe Hypertension (n=50)	p-value
Homocysteine (µmol/L)	12.8 ± 2.9	15.9 ± 3.8	< 0.001*
ADMA (µmol/L)	0.72 ± 0.20	0.86 ± 0.23	< 0.001*

Table 4 presents the correlation between homocysteine and asymmetric dimethylarginine (ADMA) levels in relation to the severity of hypertension. The results indicate that patients with mild hypertension (n=60) had a mean homocysteine level of 12.8 ± 2.9 µmol/L, whereas those with severe hypertension (n=50) exhibited a significantly higher mean level of 15.9 ± 3.8 µmol/L, with a p-value of < 0.001, indicating a strong statistical significance. Similarly, ADMA levels were observed to increase with the severity of hypertension, with mild hypertensive patients showing a mean of 0.72 ± 0.20 µmol/L, compared to 0.86 ± 0.23 µmol/L in those with severe hypertension, also yielding a p-value of < 0.001. These findings suggest a notable association between elevated levels of homocysteine and ADMA and the increased severity of hypertension, highlighting their potential role as biomarkers in hypertension management.

Table 5: Pregnancy Outcomes in Hypertensive and Control Groups

Outcome	Hypertensive Group (n=110)	Control Group (n=100)	p-value
Preterm Birth (%)	36 (32.7%)	12 (12%)	0.001*
Low Birth Weight (%)	40 (36.4%)	15 (15%)	< 0.001*
NICU Admission (%)	28 (25.5%)	10 (10%)	0.003*
Stillbirth (%)	5 (4.5%)	1 (1%)	0.151

Table 5 compares pregnancy outcomes between hypertensive and control groups. In the hypertensive group (n=110), the incidence of preterm birth was 36 cases, representing 32.7%, significantly higher than the control group (n=100), which had 12 cases or 12% (p-value = 0.001). The occurrence of low birth weight was also notably elevated in the hypertensive group, with 40 cases (36.4%) compared to 15 cases (15%) in the control group, yielding a highly significant p-value of < 0.001. Furthermore, NICU admissions were more frequent among hypertensive pregnancies, with 28

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cases (25.5%) versus 10 cases (10%) in the control group (p-value = 0.003). However, the difference in stillbirth rates was not statistically significant, with 5 cases (4.5%) in the hypertensive group compared to 1 case (1%) in the control group (p-value = 0.151). These findings underscore the adverse effects of hypertension on pregnancy outcomes, particularly in terms of preterm birth, low birth weight, and NICU admissions.

Discussion:

In our study, we compared the levels of homocysteine and asymmetric dimethylarginine (ADMA) between hypertensive and control groups. The hypertensive group exhibited a significantly elevated mean homocysteine level of 14.3 ± 3.5 µmol/L, compared to 8.7 ± 2.1 µmol/L in the control group ($p < 0.001$). Similarly, ADMA levels were higher in the hypertensive group at 0.78 ± 0.21 µmol/L, versus 0.49 ± 0.18 µmol/L in controls, with a p-value of < 0.001.

Consistent with our findings, several studies have reported elevated homocysteine levels in hypertensive pregnant women compared to their normotensive counterparts. Kharb et al. (2016) documented significantly higher homocysteine levels in both maternal and cord blood of preeclamptic women ($p<0.001$ and $p<0.01$, respectively). [6] Similarly, Chulkov et al. (2006) found that pregnant women with chronic hypertension maintained higher homocysteine levels throughout their pregnancies compared to those without hypertension. Bobić (2016) also reported an increase in mean homocysteine levels, with a difference of 0.744 µmol/L noted in preeclamptic women ($p<0.0001$)[7,8] Wadhwani et al. (2016) further corroborated this trend, showing higher homocysteine levels in preeclamptic women across various stages of pregnancy ($p<0.05$).[9]

In contrast, the findings regarding ADMA levels have been more variable. While Demir et al. (2012) reported significantly elevated ADMA levels in preeclamptic women, Rijvers et al. (2013) found only minor differences in ADMA levels between hypertensive and normotensive pregnancies. [10,11] Atamer et al. (2008) found no significant differences in ADMA levels between hypertensive and normotensive subjects, although this study was not specific to pregnancy.[12] Additionally, Laskowska et al. (2013) observed a positive correlation between homocysteine and ADMA levels in preeclamptic women with appropriate-for-gestational-age fetuses, but not in those experiencing intrauterine growth restriction. [13]

In our study, we examined homocysteine and asymmetric dimethylarginine (ADMA) levels across different types of hypertensive disorders. The mean homocysteine levels were 13.2 ± 3.1 µmol/L in the gestational hypertension group, 14.8 ± 3.4 µmol/L in the preeclampsia group, and 16.1 ± 4.2 µmol/L in the eclampsia group. Although there was a trend of increasing levels from gestational hypertension to eclampsia, these differences were not statistically significant ($p = 0.075$). Similarly, mean ADMA levels rose gradually, with values of 0.72 ± 0.19 µmol/L in gestational hypertension, 0.81 ± 0.22 µmol/L in preeclampsia, and 0.89 ± 0.24 µmol/L in eclampsia; however, this difference was also not statistically significant ($p = 0.101$).

In normal pregnancies, Maruta et al. (2017) found that maternal ADMA levels significantly increased with advancing gestational age, whereas homocysteine levels initially decreased from early to mid-gestation before rising from mid- to late-gestation[14]. For hypertensive disorders of pregnancy (HDP), maternal homocysteine levels during early gestation were significantly higher compared to those in normal pregnancies. Notably, a maternal homocysteine level exceeding 7.2 µmol/L in early pregnancy was independently linked to the development of HDP (Maruta et al., 2017). [14]

In preeclampsia, mean serum levels of both homocysteine and ADMA were significantly elevated compared to healthy controls. Specifically, Demir et al. (2012) noted that in cases of mild preeclampsia, homocysteine and ADMA levels were significantly higher, while nitric oxide (NO) levels were lower compared to controls. [10] Additionally, a significant positive correlation between maternal serum homocysteine and ADMA levels was reported in healthy normotensive pregnancies ($R = 0.38$, $p = 0.002$) and in preeclamptic patients with appropriate-for-gestational-age fetuses ($R = 0.45$, $p = 0.004$). However, this correlation was not significant in pregnancies complicated by intrauterine growth restriction, either in isolation or during severe preeclampsia (Laskowska et al., 2013). [13]

In our study, we investigated the correlation between homocysteine and asymmetric dimethylarginine (ADMA) levels in relation to hypertension severity. Patients with mild hypertension (n=60) had a mean homocysteine

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level of 12.8 ± 2.9 μmol/L, while those with severe hypertension (n=50) showed a significantly higher mean level of 15.9 ± 3.8 μmol/L ($p < 0.001$). Similarly, ADMA levels increased with hypertension severity, with mild hypertensive patients averaging 0.72 ± 0.20 μmol/L, compared to 0.86 ± 0.23 μmol/L in severe cases ($p < 0.001$).

Several studies have similarly explored the relationship between homocysteine, ADMA, and hypertension severity in pregnant women. For instance, Laskowska et al. (2013) identified a strong positive correlation between maternal serum homocysteine and ADMA levels in healthy normotensive pregnant women ($R = 0.38$, $p = 0.002$) and in preeclamptic patients with appropriate-for-gestational-age fetuses ($R = 0.46$, $p = 0.004$). [13] This correlation suggests a potential mechanistic link between elevated levels of these biomarkers in preeclampsia. Additionally, Mao et al. (2010) reported a highly significant positive correlation between plasma concentrations of homocysteine and ADMA in preeclamptic women ($r = 0.853$, $p < 0.001$).[15] They also found significant negative correlations between plasma nitric oxide (NO) concentrations and both homocysteine ($r = -0.870$, $p < 0.001$) and ADMA ($r = -0.895$, $p < 0.001$). These relationships persisted even among preeclamptic patients, indicating a strong link between these markers and disease severity.

However, some studies have produced contradictory results. In cases of pregnancies complicated by intrauterine growth restriction, the correlation between homocysteine and ADMA was not significant, even during severe preeclampsia (Laskowska et al., 2013). This finding suggests that while the relationship between homocysteine and ADMA is crucial in preeclampsia, it may not encompass all mechanisms involved in pregnancy complications. [13]

Conclusion:

In conclusion, our study highlights significant differences in demographic characteristics and biomarkers between hypertensive and control groups, particularly regarding elevated levels of homocysteine and ADMA, which are associated with the severity of hypertension. Additionally, the hypertensive group experienced notably poorer pregnancy outcomes, including higher rates of preterm birth, low birth weight, and increased NICU admissions. These findings emphasize the detrimental impact of hypertension on maternal and fetal health, warranting enhanced monitoring and management for affected pregnancies.

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