ORIGINAL RESEARCH ARTICLE

Correlation of Hyperhomocysteinemia with the Severity of Pregnancy-induced Hypertension—A Case–Control Study

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Abstract

Background: Hypertension is the most common medical problem encountered during pregnancy and is a major cause of maternal morbidity and mortality. Serum homocysteine-mediated vascular changes are similar to those associated with preeclampsia and, hence, hypothesized to be associated with this condition. The present study is being undertaken to study the association of serum homocysteine with pregnancy-induced hypertension (PIH) and folic acid supplementation.

Materials and methods: This is a prospective study conducted in a tertiary care teaching hospital in Punjab. The study was carried out for a period of 2 years. This study included 60 pregnant women, out of which 30 subjects were having hypertensive disorders of pregnancy and 30 were normotensive subjects. Fasting serum homocysteine levels were obtained, compared, and analyzed. The test was based on an immunoassay technique. The normal range of serum homocysteine was taken as 5–15 µmol/L.

Results: In this study, serum homocysteine levels were found to be higher in hypertensive subjects as compared to that in normotensive subjects. The levels of serum homocysteine were higher in severe forms of PIH in comparison to nonsevere forms. Also, the level of serum homocysteine was associated with folic acid supplementation.

Conclusion: In summary, the present study has shown an increased level of serum homocysteine in both mild and severe preeclampsia compared with normal pregnancy and a statistically significant association of total homocysteine concentrations with the severity of the disease.

Keywords: Folic acid, Homocysteine, Preeclampsia, Pregnancy-induced hypertension, HELLP syndrome.

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Introduction

Hypertension is the most common medical problem encountered during pregnancy.

Preeclampsia, a pregnancy-specific syndrome, is a major cause of maternal and perinatal morbidity and mortality with a worldwide incidence of 5 to 8% of all pregnancies.[1]

Gestational hypertension is a new hypertension developing after 20 weeks without significant proteinuria (>300mg protein in a 24-hour urine collection or >30mg/mol in a spot urinary protein:creatinine sample).

Preeclampsia is a new hypertension developing after 20 weeks with significant proteinuria.

Severe preeclampsia is preeclampsia with severe hypertension (≥ 160/110 mm Hg) and/or with symptoms (severe headache; vision problems, such as blurring or flashing before the eyes; severe pain just below the ribs; vomiting; and sudden swelling of the face, hands, or feet), and/or biochemical and/or hematological impairment.

Eclampsia is a convulsive condition associated with preeclampsia.

HELLP syndrome is hemolysis, elevated liver enzymes, and low platelet count.

How pregnancy incites or aggravates hypertension remains unresolved despite decades of research. There are many theories about the etiology and pathogenesis of preeclampsia including endothelial dysfunction, inflammation, and angiogenesis.

Toxic factors released by the placenta cause endothelial cell dysfunction by directly affecting endothelial cells or by stimulating maternal oxidative stress and inflammatory cytokines.

Oxidative stress is the imbalance of antioxidants (e.g., high density lipoprotein (HDL) and transferrin) and prooxidants. Important prooxidants are homocysteine and low density lipoprotein (LDL). Oxidative stress leads to the formation of oxygen-free radicals and lipid peroxides, which are highly reactive and are directly toxic to the endothelial cells.

With this endothelial damage, there is decreased production of vasodilators (prostacyclin) and inactivation of circulating vasodilators (nitric oxide), ultimately leading to vasospasm.

The homocysteine-mediated vascular changes are similar to those associated with preeclampsia, therefore, a hypothesis has been proposed that hyperhomocysteinemia may be associated with this condition.[2]

Homocysteine is a sulfur-containing essential amino acid primarily derived from demethylation of dietary methionine required for the growth of cells and tissues in the human body.[3]

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Homocysteine concentrations are tightly regulated by two main enzymatic pathways. Homocysteine can be remethylated to methionine by a pathway requiring folic acid as a methyl donor. In addition to adequate folic acid, the pathway requires vitamin B12 as an important cofactor. Alternatively, homocysteine can be removed by transsulfuration, a pathway dependent on the cofactor vitamin B6.[4]

High concentrations of plasma total homocysteine are associated with serious pregnancy complications, including PIH, preeclampsia,[5] and placental abruption.[6]

Higher maternal total homocysteine concentration is associated with a small increased risk for small for gestational age offsprings.[7]

It is one of the leading causes of maternal mortality, but the etiopathology of preeclampsia is still an enigma. One metabolic effect of folate deficiency is an elevated plasma homocysteine concentration. It is not yet known whether an elevated total homocysteine concentration is harmful by itself through its vascular effect or is merely a reflection of the folate status. Hence, this study was done to see the association of homocysteine and folic acid with hypertensive disorders of pregnancy.

Materials and Methods

This prospective study was conducted in the Department of Obstetrics and Gynaecology, at a tertiary care hospital and medical college, Amritsar, Punjab. The study group included 60 pregnant subjects, including 30 subjects with hypertensive disorders of pregnancy presenting in outdoor or emergency as cases and 30 normotensive subjects enrolled for normal antenatal care as controls.

Inclusion Criteria

Hypertensive pregnant females with a gestation period more than or equal to 20 weeks.

Exclusion Criteria

- Chronic hypertension, renal or liver disease, h/o thromboembolism, h/o smoking, h/o intake of anticoagulant therapy, h/o medical illness causing a prethrombotic state, multiple pregnancies, molar pregnancy, and h/o epilepsy in the prepregnancy state.

Control Group

Normotensive patients with a gestational age more than or equal to 20 weeks.

Study Group

Patients with hypertensive disorders of pregnancy with and without treatment presenting beyond 20 weeks of gestation with blood pressure more than or equal to 140/90 mm Hg.

All patients meeting the inclusion criteria were enrolled, and after taking their written informed consent, a detailed history was taken including complaints during the present pregnancy, past history, menstrual history, and obstetric history. Detailed general physical examination and obstetric examination were done.

Five milliliters of the venous sample were collected in a red-topped vacutainer and processed for serum homocysteine. A fasting sample of serum homocysteine was taken. The sample so collected was placed immediately on ice and the serum separated within 1 hour of collection. The test was based on an immunoassay technique.

The normal range of serum homocysteine was taken as 5–15 µmol/L.

Patients of both the groups were followed up, and their data were collected, collated, and analyzed thoroughly. The maternal condition was assessed clinically and by ultrasound and Doppler velocimetry. Peripheral blood film, liver function tests, and complete blood counts were analyzed to confirm the diagnosis of HELLP syndrome along with the alarming symptoms in the subjects.

The decision for termination was made on the basis of gestational age and maternal and fetal status.

The data so collected were statistically analyzed.

Statistical Analysis

The recorded data were analyzed using SPSS version 20. Statistical tests applied were Pearson's Chi-square test, Student's *t*-test, and one-way analysis of variance (ANOVA).

Results

In our study, among the 30 hypertensive subjects (cases), 21 (70%) had a normal serum homocysteine (< 15 µmol/L), while 9 subjects (30%) had hyperhomocysteinemia (> 15 µmol/L).

On comparing this with 30 normotensive subjects (controls), 29 subjects (96.60%) had serum homocysteine within the normal range, while only 1 subject had hyperhomocysteinemia. This comparison was found to be statistically significant (Table 1).

We found that the mean value of serum homocysteine was 14.65 + 9.247 µmol/L among the 30 cases (hypertensive subjects), whereas the mean serum homocysteine was 8.63 + 3.71 µmol/L in controls (normotensive subjects). This difference was statistically significant (Table 2).

Among the 30 hypertensive subjects (cases), 18 subjects who had a positive history of intake of folic acid supplementation in the antenatal period of the present pregnancy had a mean serum homocysteine of 10.31 + 6.31 µmol/L, whereas 12 subjects in the same group who did not receive any folic acid supplementation had a higher mean serum homocysteine of 12.16 + 12.77 µmol/L. This comparison was found to be statistically significant. On comparing them with controls, all the subjects had folic acid supplementation in the antenatal period and their mean serum homocysteine was found to be 8.63 + 3.71 µmol/L, which was less than the mean serum homocysteine in the cases (Table 3).

All the normotensive subjects (n = 30) had a mean serum homocysteine of 8.41 + 3.57 µmol/L. Out of the 30 hypertensive subjects, 7 subjects had gestational hypertension, with a mean serum homocysteine of 8.18 + 3.79 µmol/L, whereas 5 subjects who had mild preeclampsia had a mean serum homocysteine of 8.85 + 5.57 µmol/L. On analysis, these data were not found to be statistically significant (Table 4).

Among the 30 hypertensive subjects, 7 had gestational hypertension with a mean serum homocysteine of 8.18 + 3.79 µmol/L, 5 subjects had mild preeclampsia with a mean serum homocysteine of 8.85 + 5.57 µmol/L, 11 had severe preeclampsia with a mean serum homocysteine of 9.93 + 5.10 µmol/L, 3 subjects who developed HELLP syndrome had a mean serum homocysteine of 19.63 + 26.29 µmol/L, and 4 subjects who developed eclampsia had a mean serum homocysteine of 16.06 + 4.68 µmol/L. This correlation was found to be statistically significant (Table 5).

Table 1: Incidence of hyperhomocysteinemia in cases and controls

Serum homocysteine	*Cases (n = 30)*	*Control (n = 30)*	*p value*
< 15 µmol/L	21 (70%)	29 (96.60%)	0.012*
> 15 µmol/L	9 (30%)	1 (3.33%)	
Total	100%	100%	

$p > 0.05$, not significant; *$p < 0.05$, significant

Table 2: Comparison of mean serum homocysteine between cases and controls

Variables	*Group*	*N*	*Mean*	*Standard deviation*	*p value*
Serum homocysteine	Cases	30	14.65	9.247	0.010*
	Controls	30	8.63	3.71	

$p > 0.05$, not significant; *$p < 0.05$, significant

Table 3: Correlation of folic acid intake with serum homocysteine levels in cases and controls

Groups	*Folic acid intake*	*Number*	*Mean homocysteine*	*Standard deviation*	*p value*
Cases	Yes	18 (60%)	10.31	6.31	0.047*
	No	12 (40%)	12.16	12.77	
Controls	Yes	30 (100%)	8.63	3.71	–
	No	0	–	–	

$p > 0.05$, not significant; *$p < 0.05$, significant

Table 4: Comparison of mean serum homocysteine in normotensive subjects and subjects of non severe forms of PIH

Variables	*n*	*Mean homocysteine*	*Standard deviation*	*p value*
Normotensive	30	8.41	3.57	0.7 (NS)
Gestational hypertension	7	8.18	3.79	
Mild preeclampsia	5	8.85	5.57	

$p > 0.05$, not significant; $p < 0.05$, significant

Table 5: Correlation of mean serum homocysteine with grades of PIH

Grade of PIH	*No*	*Mean homocysteine*	*Standard deviation*	*p value*
Gestational hypertension	7	8.18	3.79	0.020*
Mild preclampsia	5	8.85	5.57	
Severe preeclampsia	11	9.93	5.10	
HELLP syndrome	3	19.63	26.29	
Eclampsia	4	16.06	4.68	

$p > 0.05$, not significant; *$p < 0.05$, significant

Discussion

In our study, we found that the mean value of serum homocysteine was 14.65 + 9.247 µmol/L among the hypertensive subjects, whereas the mean serum homocysteine was 8.63 + 3.71 µmol/L in the normotensive subjects. The results were similar to another study conducted by Makedos et al., who found in their study that the mean level of serum homocysteine was 11.11 µmol/L in preeclamptic women, while it was lower in normotensive subjects, i.e., 6.40 µmol/L.[8] Powers et al. in the year 2001 conducted a study and also found a similar and significant difference in the serum level of homocysteine in preeclamptic subjects and normotensive subjects.[9] Zeeman et al. in the year 2003 studied that the serum homocysteine concentration in patients with preeclampsia was higher in comparison to those with uncomplicated pregnancies.[10]

In our study, among the hypertensive subjects, those who had a positive history of intake of folic acid supplementation in the antenatal period of the present pregnancy had a mean serum homocysteine of 10.31 + 6.31 µmol/L, whereas those who did not receive any folic acid supplementation had a mean serum homocysteine of 12.16 + 12.77 µmol/L. In the control group, however, all the subjects had folic acid supplementation in the antenatal period, showing a lesser mean homocysteine concentration (8.63 + 3.71 µmol/L).

Our results were similar to another study conducted by Qureshi et al. in the year 2010, where they found a significant difference in the serum homocysteine value in the pre-supplementation and the post-supplementation group of women. Those in the pre-supplementation group had a mean serum homocysteine of 19.10 ± 4.87 µmol/L, while it was 10.01 + 1.25 µmol/L in the post-supplementation group. In a healthy pregnant woman,

the mean serum homocysteine was 14.60 + 0.25 µmol/L in the pre-supplementation group, while it was 9.12 + 0.54 µmol/L in the post-supplementation group.[11] Patrick et al. conducted a study in 2004 and found an inverse relationship between serum homocysteine and serum folate concentration in preeclampsia.[4]

Leeda et al. observed a significant reduction in the mean fasting homocysteine levels from 16.6 to 6.1 µmol/L following daily supplementation of folate for 10 weeks in women with a history of preclampsia.[12]

In our study, we found that the normotensive subjects had a mean serum homocysteine of 8.41 + 3.57 µmol/L. Out of all the hypertensive subjects, those having gestational hypertension had a mean serum homocysteine of 8.18 + 3.79 µmol/L, whereas those with mild preeclampsia had a mean serum homocysteine of 8.85 + 5.57 µmol/L. Our study was similar to another study conducted by Haranzadeh et al. in 2008, in which they concluded that there is no significant difference in the mean serum homocysteine level between normotensive pregnant women (8.8 + µmol/L *vs* 10.4 + 2.3 µmol/L) and women with mild preeclampsia.[13]

In our study, out of all hypertensive subjects, those who had mild preeclampsia had a mean serum homocysteine of 8.85 + 5.57 µmol/L, subjects with severe preeclampsia had a mean serum homocysteine of 9.93 + 5.10 µmol/L, those who developed HELLP syndrome had a mean serum homocysteine of 19.63 + 26.29 µmol/L, and lastly subjects with eclampsia had a mean serum homocysteine of 16.06 + 4.68 µmol/L. Thus, it was seen that in more severe cases of the disease, the mean value of serum homocysteine was also higher as compared to mild preeclampsia and gestational hypertension. Ingec et al., in the year 2005, also demonstrated a positive relationship between increased serum homocysteine and the severity of preeclampsia.[14] Singh et al. in 2008 supported the fact, through their study, that the severity of preeclampsia was directly related to homocysteine concentration.[15] Guven et al. conducted a study in the year 2009 and found that the mean serum homocysteine levels in subjects with mild PIH were 8.2 µmol/L, while in subjects with severe PIH, the mean value was 8.9 µmol/L.[16]

Conclusion

Since hypertensive disorders of pregnancy are one of the leading causes of maternal and neonatal morbidity and mortality, it is important to identify and reduce the modifiable risk factors associated with them; one of them being hyperhomocysteinemia, which has been shown to have implications in adverse maternal and neonatal outcomes. Folic acid is an important determinant of serum homocysteine. Hence, regular folic acid supplementation should be prescribed and measurement of serum homocysteine for the risk assessment of developing PIH can be undertaken.

References

1. Baumann MU, Bersinger NA, Surbek DV. Serum markers for predicting preeclampsia. Mol Aspects Med 2007;28:227–244.
2. Rajkovic A, Catalano PM, Malinow MR. Elevated homocyst(e)ine levels with preeclampsia. Obstet Gynaecol 1997;90:168–171.
3. Refsum H, Ueland PM, Nygard O, et al. Homocysteine and cardiovascular disease. Annu Rev Med 1998;49:31–62.
4. Patrick TE, Powers RW, Daftary AR, et al. Homocysteine and folic acid are inversely related in black women with Preeclampsia. Hypertension 2004;43:1279–1282.
5. Dekker GA, de Vries JI, Doelitzsch PM, et al. Underlying disorders associated with severe early-onset preeclampsia. Am J Obstet Gynecol 1995;173:1042–1048.
6. Goddijn-Wessel TAW, Wouters MGAJ, van de Molen EF, et al. Hyperhomocysteinemia: a risk factor for placental abruption or infarction. Eur J Obstet Gynaecol Reprod Biol 1996;66:23–29.
7. Hogeveen M, Blom HJ, den Heijer M, et al. Maternal homocysteine and small for gestational age offspring: systematic review and meta-analysis. Am J Clin Nutr 2012;95:130–136.
8. Makedos G, Papaniculaou A, Hitoglou A, et al. Homocysteine, folic acid and B12 serum levels in pregnancy complicated with pre eclampsia. Arch Gynecol Obstet 2007;275:121–124.
9. Powers RW, Evans RW, Ness RB, et al. Homocysteine and cellular fibronectin are increased in preeclampsia, not transient hypertension of pregnancy. Hypertens Pregnancy 2001;(20):69–77.
10. Zeeman GG, Alexander JM, Mcintire DD, et al. Homocysteine plasma concentration levels for the prediction of preeclampsia in women with chronic hypertension. Am J Obstet Gynecol 2003;189:574–576.
11. Qureshi SB, Ahmad M, Qureshi PM, et al. Hyperhomocysteinemia, vascular related pregnancy complications and the response to vitamin supplementation in pregnant women of Pakistan. J Pak Med Assoc 2010;60(9):741–745.
12. Leeda M, Riyazi N, de Vriesa JI, et al. Effects of folic acid and vitamin B6 supplementation on women with hyperhomocysteinemia and history of preeclampsia or fetal growth restriction. Am J Obstet Gynecol 1998;179:135–139.
13. Hasanzadeh M, Ayatollahi H, Farzadnia M, et al. Elevated plasma total homocysteine in preeclampsia. Saudi Med J 2008;29(6):875–878.
14. Ingec M, Borekci B, Kadanali S. Elevated plasma homocysteine concentrations in severe preeclampsia and eclampsia. Tohoku J Exp Med 2005;206(3):225–231
15. Singh U, Gupta HP, Singh RK, et al. A study of changes in homocysteine levels during normal pregnancy and pre-eclampsia. J Indian Med Assoc 2008;106(8):503–505.
16. Guven MA, Coskun A, Ertaz IE, et al. Association of maternal serum CRP, IL-6, TNF-ALPHA, homocysteine, folic acid and vitamin B12 levels with the severity of preeclampsia and fetal birth weight. Hypertens Pregnancy 2009;28:190–200.