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HMGB1 Modulates Angiogenic Imbalance and Cardiovascular Complications in Preeclampsia through Decorin and VEGF Regulation

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Abstract

Background: Preeclampsia (PE) is a serious multisystem disorder that ranks among the leading causes of maternal and neonatal morbidity and mortality. The condition is characterized by an angiogenic imbalance, which has adverse effects on fetal development and contributes to an increased risk of cardiovascular disease in the long term. This study aims to explore the connection between sterile inflammation mediated by HMGB1 and angiogenic imbalance in PE by examining key markers such as HMGB1, VEGF, Decorin, and TGF-β.

Methods: In an animal model of PE, we measured the levels of HMGB1, VEGF, Decorin, and TGF-β in plasma, placenta, and heart tissues using ELISA. Additionally, Decorin levels were assessed through immunofluorescence in trophoblasts.

Results: We found that levels of Decorin and TGF-β were significantly elevated in the plasma, placenta, and heart tissues of PE animals compared to non-pregnant and pregnant controls, whereas VEGF levels were reduced. Treatment with Glycyrrhizic acid (GA) restored the expression levels of these markers to more normalized values in the PE groups.

Conclusion: Our findings indicate that HMGB1 plays a critical role in preeclampsia by mediating the upregulation of anti-angiogenic factors like Decorin and the downregulation of angiogenic factors like VEGF. This study highlights a significant correlation between HMGB1 and Decorin in driving the angiogenic imbalance that contributes to the pathophysiology of PE.

Keywords: Angiogenesis Inhibitors, Cardiovascular Diseases, Decorin, Transforming Growth Factor beta, High Mobility Group Box 1 Protein, Preeclampsia.

Introduction

Preeclampsia (PE) is a complex, multisystem disorder characterized by hypertension that significantly contributes to maternal and neonatal morbidity and mortality worldwide (1, 2). According to the World Health Organization, approximately 16% of maternal deaths are attributable to preeclampsia and related gestational hypertensive disorders (3). However, effective prevention and treatment strategies have not yet been established, and the only substantial treatment strategy thus far is the delivery of placenta (4). Despite extensive research, the precise etiology of PE remains elusive. It is widely accepted that inadequate trophoblast invasion plays a pivotal role in the pathogenesis of PE. The disorder is believed to stem from severe placental dysfunction, characterized by defective spiral artery remodeling and poor extravillous trophoblasts (EVTs) invasion which are driven by early angiogenic imbalances and inflammatory disorders (5-7)

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During a typical pregnancy, the maternal circulatory system undergoes significant physiological changes to support the growing fetus. These changes include increased intravascular volume and a notable reduction in vascular resistance, resulting in a slight decrease in arterial blood pressure compared to nonpregnant levels and an enhanced glomerular filtration rate (8-10). A key process in this adaptation is angiogenesis, which is tightly regulated by a balance of endogenous angiogenic and angiostatic factors (11). Disruption of this balance is believed to contribute to the pathogenesis of preeclampsia. In particular, the anti-angiogenic factor soluble fms-like tyrosine kinase-1 (sFlt1), which is overexpressed in the placenta during preeclampsia, antagonizes the effects of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), leading to increased peripheral vascular resistance and elevated arterial pressure (12). The regulatory effects of decidua-derived transforming growth factor beta (TGF-β) and Decorin (DCN) play an important role in EVT proliferation, migration, and invasion (13). DCN, a small leucine-rich proteoglycan secreted by stromal cells, including endometrial and chorionic villous interstitial cells, plays a crucial role in regulating angiogenesis. By binding to VEGF receptor-2 (VEGFR-2) on EVTs, DCN inhibits cell proliferation and angiogenesis, suggesting that it may contribute to the pathophysiology of PE through these mechanisms (14).

Vascular endothelial growth factor (VEGF), a potent pro-angiogenic factor, stimulates angiogenesis by recruiting stromal cells that support this process and secrete additional VEGF (15). Along with TGF-β, DCN acts as a negative regulator of angiogenesis by blocking VEGF, which is essential for the stabilization of endothelial cells in mature blood vessels (16). The impaired angiogenesis in preeclampsia, therefore, has significant implications for maternal and fetal health. Clinically, preeclampsia is often marked by atypical signs and rapid disease progression, which creates challenges in diagnosis and management. Moreover, the angiogenic imbalance observed in preeclampsia is associated with an increased long-term risk of cardiovascular disease (CVD) in affected women.

This study explores the potential link between sterile inflammation, mediated by high-mobility group box 1 (HMGB1) and the angiogenic imbalance observed in preeclampsia. Understanding this connection could provide new insights into the pathogenesis of preeclampsia (PE) and highlight novel therapeutic targets for mitigating the long-term cardiovascular risks associated with this disorder.

Materials and Methods

Animals

Wistar rats (250–300 g) were procured from the animal house, Jamia Hamdard, New Delhi. All the experiments were performed after permission from the Institutional Animal Ethical Committee (IAEC) of Jamia Hamdard, New Delhi, India. We adhered to the standards of the Committee for Control and Supervision of Experiments on Animals (CPCSEA), Government of India. During the experiment, the rats were kept in a room with a constant temperature, humidity, and light cycle (12 hours of light and 12 hours of darkness). They had free access to tap water and food provided ad libitum.

The animal model of preeclampsia was developed as described by Huma et al (17) and organs were harvested after perfusion. The plasma was separated from blood by centrifugation at 625 G and stored at -20 °C till further use. One part of the placenta and heart was snap-frozen in liquid nitrogen immediately after collection for further processing, and the other part was fixed in 10% formalin for sectioning.

Preparation of tissue lysate

The target tissues (heart and placenta) were dissected with sterile instruments on ice as quickly as possible to avoid protease

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degradation, and stored in microcentrifuge tubes with a circular bottom stored at -80 °C. The frozen samples were weighed and for 100 mg tissue samples 1 ml of ice-cold RIPA buffer, 0.5 ml Phenyl methane sulfonyl fluoride PMSF (Sigma, Catalog No # 329-98-6, USA), and 1µl 100X Protease Inhibitor cocktail (PIC) (Sigma, Catalog No # P8849-1ML USA) was added and homogenized with an electric homogenizer. After homogenization, prepared tissue lysate was centrifuged at 30,000 G for 20 minutes and 4 °C. The supernatant was aspirated and transferred to a new tube, which was also maintained on ice. This lysate is further processed for Enzyme-Linked Immunosorbent Assay (ELISA) as per the manufacturer's instructions.

Estimation of angiogenic/anti-angiogenic markers

ELISA was performed to estimate the level of inflammatory markers such as HMGB1 (Catalog No # E-EL-R0505, USA), VEGF (Catalog No # E-EL-R2603, USA), TGF-β (Catalog No # E-EL-R0084, USA), and DCN (Catalog NO # E-EL-R0321, USA). The kits for ELISA were procured from R & D Elabsciences (USA) and the assays were performed according to the manufacturer's instructions. These kits recognize rat antibodies in the given samples. No significant cross-reactivity or interference between rat antibodies and analogs was noted.

Immunofluorescence (IF)

Placental tissues collected from normal pregnant and PE pregnant rats were fixed, sectioned, and fluorescence stained to visualize the expression of sterile inflammatory and endothelial dysfunction markers, specifically Decorin. 4′, 6-diamidino-2-phenylindole (DAPI) (Sigma, Catalog No # 62247, USA) was used as a nuclear stain in all experiments. Following antigen retrieval, the sections were incubated in a blocking solution for 30 to 45 minutes at room temperature (5% bovine serum albumin and 0.3 percent Triton-X 100 in PBS). After adding primary antibodies, the slides were incubated at 4 °C overnight. Secondary antibodies were added and incubated at room temperature for 2 hours (about 25 °C), after which the nuclei were stained with DAPI. All immunofluorescence (IF) staining was done in complete darkness. Slides were prepared by photographing four to six random fields at 100 X magnification using Confocal Laser Scanning Microscopy (Leica Microsystems, Germany) model SPE (scale bar: 25 µm).

Statistical Analysis

Data are expressed as the mean ± the standard error of the mean (SEM). The statistical analysis of differences between experimental groups was performed by one-way analysis of variance (ANOVA). A p-value of <0.05 was considered statistically significant. Further statistical analysis was performed by Tukey's multiple-comparison test.

Results

Measurement of HMGB1 in the heart

To gain insights into the role of HMGB1 in mediating CVDs in LNAME-induced preeclamptic rats, the expression of HMGB1 was detected in the heart tissue of rats from all groups. The expression of HMGB1 was increased in the hearts of PE rats and was significantly reduced by GA treatment (Fig. 1).

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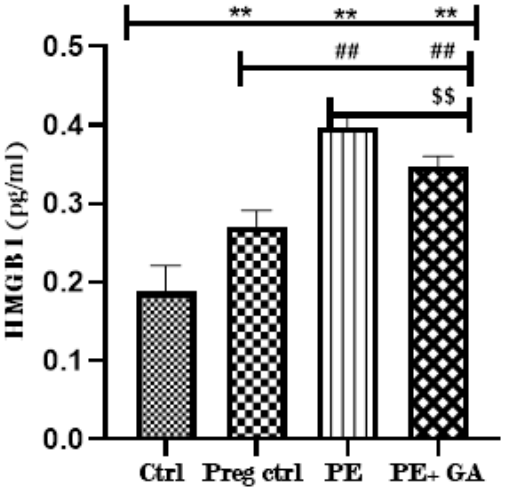

Fig. 1. Expression of HMGB1 in heart tissue of nonpregnant (control), pregnant (Preg Ctrl), pregnant + L-NAME (PE), and Preeclamptic + GA (PE+GA) rats. L-NAME and GA stand for N^G-nitro-L-arginine-methyl-ester and Glycyrrhizic acid respectively. Values are expressed as Mean ± SEM. The result is significant with*p-value<0.05, **p-value < 0.01 as compared to control; $^{\#}$p-value <0.05, $^{\#\#}$p-value <0.01 as compared to Preg Ctrl; and $^{\$}$p-value <0.05, $^{\$\$}$p-value < 0.01 as compared to PE.

Measurement of VEGF

Vascular endothelial growth factor (VEGF) levels in the plasma (Fig. 2A), placenta (Fig. 2B), and heart (Fig. 2C), of the L-NAME induced animal model (PE) (plasma: 147.94 ± 5.74 pg/ml, placenta: 210.5 ± 4.9 pg/ml, and heart: 91.93 ± 3.14 pg/ml *p-value <0.05) non-pregnant control (Ctrl) (plasma: 195.22 ± 2.6 pg/ml, Placenta: NA , and heart:124.4 ± 4.3 pg/ml, *p-value <0.05), pregnant control (Preg Ctrl) (plasma: 220.8 ± 8.6 pg/ml, placenta: 314.2 ± 7.3 pg/ml, and heart: 135.2 ± 4.6 pg/ml, *p- value < 0.05), and PE rats administered with GA (PE+GA) (plasma:198.89 ± 4.4 pg/ml, placenta: 279.99 ± 6.03 pg/ml, and heart: 109.5 ± 3.75 pg/ml, *p-value <0.05) were estimated to investigate the potential role of HMGB1 in establishing an anti-angiogenic state in PE. Compared with the non-pregnant and pregnant control groups, decreased VEGF level expression was observed in PE groups. GA treatment further increased the expression of VEGF in PE groups in the plasma, placenta, and heart of the animal models.

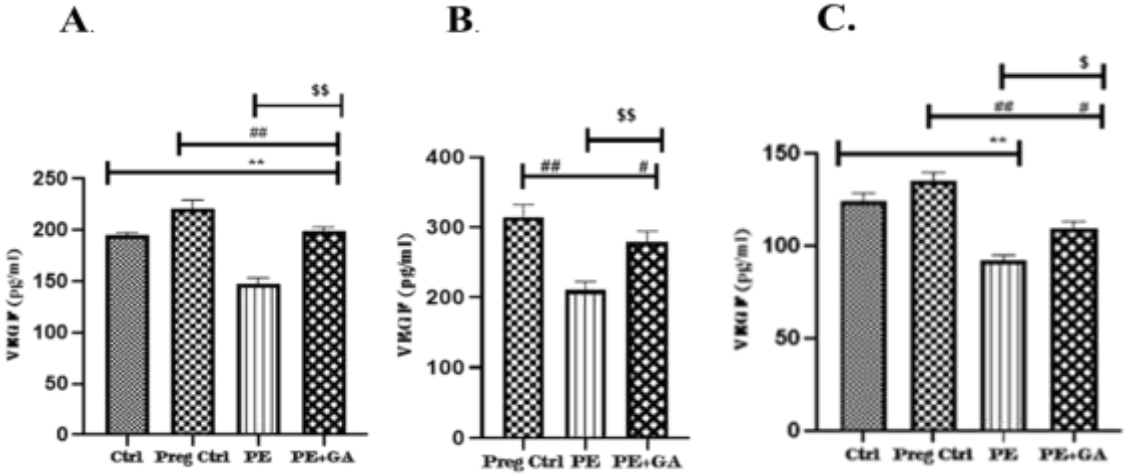

Fig. 2. Estimation of VEGF in the (A) plasma, (B) placenta, and (C) heart tissue of the L-NAME-induced animal model of PE in nonpregnant (control), pregnant (Preg Ctrl), pregnant + L-NAME (PE), and Preeclamptic + GA (PE+GA) rats. L-NAME and GA stand for N^G-nitro-L-arginine-methyl-ester and Glycyrrhizic acid respectively. Values are expressed as Mean ± SEM. The result is significant with*p-value<0.05, **p-value < 0.01 as compared to control; $^{\#}$p-value <0.05, $^{\#\#}$p-value <0.01 as compared to Preg Ctrl; and $^{\$}$p-value <0.05, $^{\$\$}$p-value < 0.01 as compared to PE. Abbreviations are explained in the text.

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Measurement of TGF-β

The central role of HMGB1 in an angiogenic imbalance in PE was investigated by evaluating the TGF-β levels in the plasma (Fig. 2A), placenta (Fig. 2B), and heart (Fig. 2C), of the L-NAME induced animal model (PE) (plasma:117.55 ± 3.11 pg/ml, placenta: 45.13 ± 0.83 pg/ml, and heart: 23.71 ± 0.76 pg/ml, *p-value <0.05) non-pregnant control (Ctrl) (plasma: 25.9 ± 0.4 pg/ml placenta: NA, and heart: 5.11± 0.3 pg/ml, *p-value <0.05), pregnant control (Preg Ctrl) (plasma: 36.59 ± 1.06 pg/ml, placenta: 16.9 ± 0.23 pg/ml, and heart: 12.75 ± 0.6 pg/ml, *p-value <0.05) and PE rats administered with GA (PE+GA) (plasma: 64.71 ± 0.33 pg/ml, placenta: 24.0 ± 1.7 pg/ml, and heart: 19.87 ± 0.79 pg/ml, *p-value <0.05). Compared with the non-pregnant and pregnant control group, increased TGF-β expression was observed in the PE groups. GA treatment decreased expression of TGF-β in PE groups.

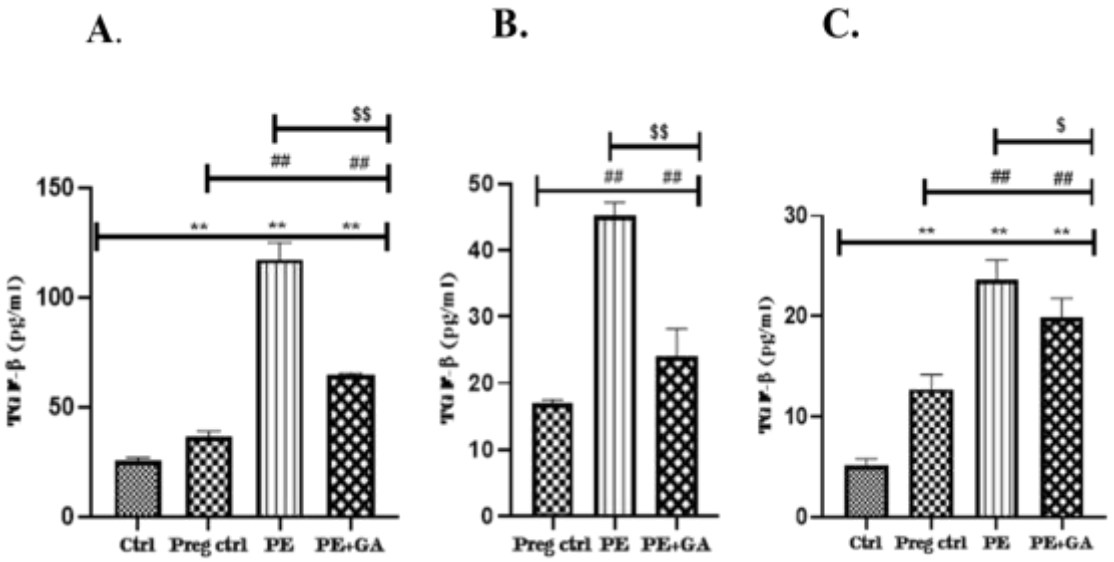

Fig. 3. Estimation of TGF-β in the (A) plasma, (B) placenta, and (C) heart tissue of the L-NAME-induced animal model of PE in nonpregnant (control), pregnant (Preg Ctrl), pregnant + L-NAME (PE), and Preeclamptic + GA (PE+GA) rats. L-NAME and GA stand for N^G-nitro-L-arginine-methyl-ester and Glycyrrhizic acid respectively. Values are expressed as Mean ± SEM. The result is significant with*p-value<0.05, **p-value < 0.01 as compared to control; $^{\#}$p-value <0.05, $^{\#\#}$p-value <0.01 as compared to Preg Ctrl; and $^{\$}$p-value <0.05, $^{\$\$}$p-value < 0.01 as compared to PE. Abbreviations are explained in the text.

Measurement of decorin

The potential role of HMGB1 in mediating angiogenic imbalance in the PE animal model was assessed by evaluating decorin levels in the plasma (Fig. 4A), placenta (Fig. 4B), and heart (Fig. 4C) of the L-NAME induced animal model (PE) (plasma: 14.1 ± 1.003 pg/ml, placenta: 22.2 ± 0.95 pg/ml, and heart: 29.11 ± 1.95 pg/ml, *p-value <0.05), non-pregnant control (Ctrl) (plasma: 2.643 ± 0.45 pg/ml, placenta: NA, and heart: 9.34 ± 0.71 pg/ml, *p- value <0. 05), pregnant control (Preg Ctrl) (plasma: 3.08 ± 0.5 pg/ml, placenta: 3.5 ± 0.54 pg/ml, and heart: 16.91 ± 1.66 pg/ml, *p-value <0.05), and PE rats administered with GA (PE+GA) (plasma: 7.5 ± 0.52 pg/ml, placenta: 15.98 ± 1.07 pg/ml, and heart: 20.36 ± 1.1 pg/ml, *p-value <0.05) . Compared with the nonpregnant and pregnant control groups, increased decorin level expression was observed in the PE groups. GA treatment decreased expression in PE groups.

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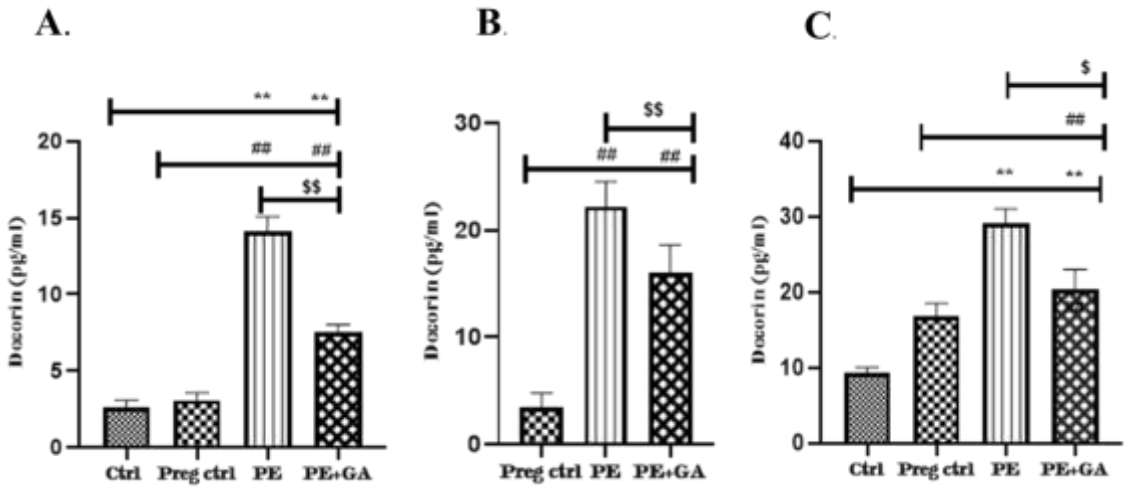

Fig. 4. Estimation of decorin in the (A) plasma, (B) placenta, and (C) heart tissue of the L-NAME-induced animal model of PE in nonpregnant (control), pregnant (Preg Ctrl), pregnant + L-NAME (PE), and Preeclamptic + GA (PE+GA) rats. L-NAME and GA stand for N^G-nitro-L-arginine-methyl-ester and Glycyrrhizic acid, respectively. Values are expressed as Mean ± SEM. The result is significant with*p-value<0.05, **p-value < 0.01 as compared to control; $^{\#}$p-value <0.05, $^{\#\#}$p-value <0.01 as compared to Preg Ctrl; and $^{\$}$p-value <0.05, $^{\$\$}$p-value < 0.01 as compared to PE. Abbreviations are explained in the text.

Expression of decorin

Decorin protein was expressed in the placentae of both Preg Ctrl and PE rats, as shown by the red immunofluorescence staining in the trophoblast layer of the placenta (Fig. 5). We observed that the expression of decorin was mostly extracellular in PE placentae (Fig. 5e) while in Preg Ctrl, the expression was intra-nuclear (Fig. 5b) as shown by merged images of DAPI and red immunostaining. It is evident from the IF studies that the decorin expression was attenuated by GA administration in the trophoblasts of PE+ GA rats (Fig. 5h).

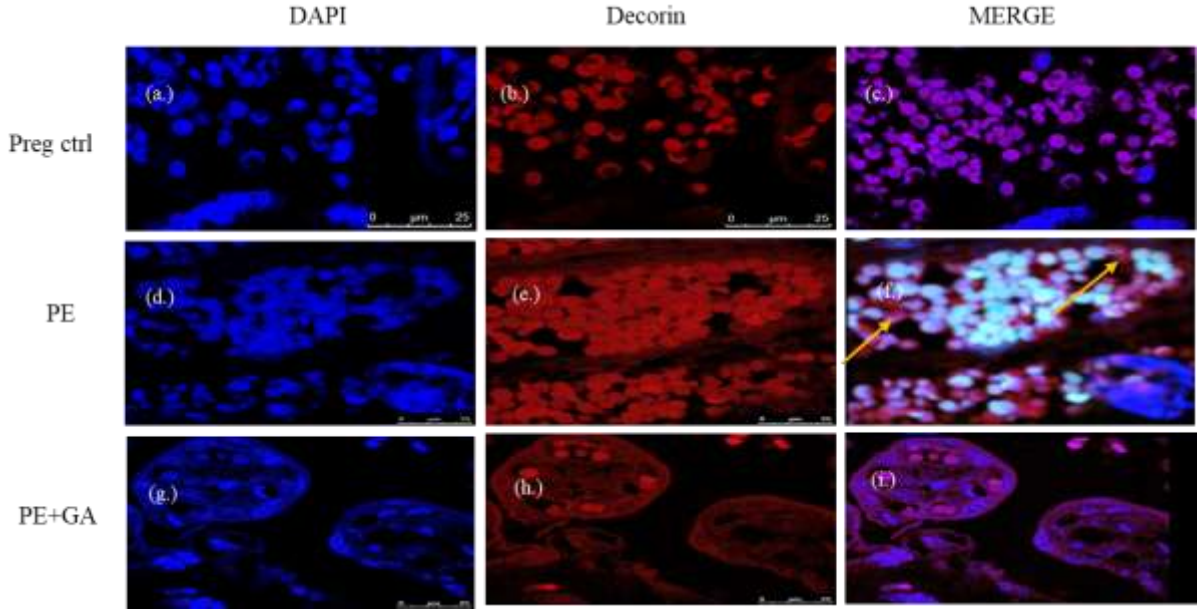

Fig. 5. Expression of decorin in placentae by IF in placentae of pregnant (Preg Ctrl), pregnant + L-NAME (PE), and Preeclamptic + GA (PE+GA) groups. Nuclear (blue) staining by DAPI (a, d, g), (a, d, g), (a, d, g), and expression of HMGB1 (b, e, h) by red. (c, f, i) panels are merged images of decorin and DAPI staining. The yellow arrowheads indicate extranuclear expression of decorin, which is attenuated by GA, as depicted in panel (i). Scale bar: 25 µm.

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Discussion

In our study, we observed that the levels of angiogenic and anti-angiogenic markers were significantly altered in the plasma, placenta, and heart tissues in the L-NAME-induced animal model of preeclampsia. These findings align with previous studies that have similarly reported an imbalance in these markers as a hallmark of preeclampsia, contributing to placental dysfunction and maternal systemic complications. The increase in proinflammatory cytokines and antiangiogenic factors observed in our model mirrors the progressive immune activation characteristic of preeclampsia, as documented in the literature (7). Notably, our results also underscore the long-term cardiovascular risks associated with preeclampsia, as evidenced by alterations in markers expressed in heart tissue such as HMGB1, DCN, VEGF, and TGF-β, which correlate with findings in other studies that linking preeclampsia to future cardiovascular disease in affected mothers (18).

Our study demonstrates a significant association between preeclampsia and an imbalance of angiogenic and anti-angiogenic factors, which not only affect placental function but also has systemic effects, particularly on the cardiovascular system. Previous studies demonstrate that an appropriate balance of pro- and anti-angiogenic factors is needed to regulate blood vessel formation and to maintain vascular function in PE (19, 20). Our findings highlight the role of HMGB1, DCN, TGF-β, and VEGF in mediating this imbalance, contributing to the pathophysiology of preeclampsia and its associated complications.

The remodeling of uterine arteries into high-volume, low-resistance vessels during early pregnancy are crucial for proper placental function. Defects in this process leads to placental ischemia and injury, triggering the release of inflammatory molecules like HMGB1 as described by Staff et al (21). Consistent with previous studies, we observed elevated HMGB1 levels in the heart tissues of L-NAME-induced PE rats.

Further investigation into the role of DCN revealed its contribution to the angiogenic imbalance observed in PE. Our study underscores the importance of DCN in the pathogenesis of preeclampsia. The increased levels of DCN observed in the plasma, placenta, and heart tissues of PE rats emphasize the role of DCN in disrupting the delicate balance needed for normal placentation and vascular remodeling. These findings are in agreement with the studies by Lala and Nandi, which demonstrate that DCN is crucial for regulating EVT cell functions and maintaining the balance of trophoblast and decidual cell differentiation which is essential for proper spiral artery remodeling (22). In our study, we found that DCN and TGF-β levels were significantly increased in PE rats, suggesting their role in mediating the anti-angiogenic environment characteristic of the condition. Notably, when HMGB1 was blocked using GA, the levels of DCN and TGF-β were alleviated, indicating that HMGB1 regulates DCN expression in the placenta and its release into the extracellular milieu (23). In this study, we observed a significant increase in the levels of anti-angiogenic markers DCN and TGF-β in PE rats, which were subsequently reduced in PE rats treated with GA, an HMGB1 inhibitor. These findings suggest that HMGB1 plays a regulatory role in the expression and extracellular release of DCN in the placenta. Additionally, VEGF, a crucial pro-angiogenic factor known for its role in maintaining endothelial and vascular health, was markedly decreased in the plasma and placenta of PE rats. This reduction is consistent with existing evidence linking VEGF antagonism to hypertension and proteinuria, as VEGF typically promotes the production of nitric oxide and vasodilatory prostacyclins, which help lower blood pressure and reduce vascular tone (24). Importantly, the restoration of VEGF levels in GA-treated PE rats further supports the hypothesis that HMGB1 mediates the upregulation of anti-angiogenic factors like DCN while downregulating angiogenic factors such as VEGF. These findings highlight a clear

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correlation between HMGB1 and DCN in driving the angiogenic imbalance contributing to the pathophysiology of PE.

Studies reveal that preeclampsia is associated with a significantly increased risk of future cardiovascular diseases, including coronary heart disease, heart failure, and stroke (25). Research by Huma et al. has also identified cardiac hypertrophy in PE models (17). The presence of cardiovascular complications both during and after pregnancy suggests that the cardiovascular system may be more than just a casualty of preeclampsia's poor placentation; it could also play a significant role in the disease's pathogenesis. Our findings further corroborate this by demonstrating a direct association between preeclampsia and myocardial complications, such as elevated levels of decorin and fibrosis markers like TGF-β in the L-NAME-induced PE model.

In conclusion, preeclampsia, a condition marked by trophoblast inflammation and placental hypoxia is further complicated by an angiogenic imbalance. This study focused on the role of HMGB1 in contributing to the angiogenic imbalance observed in preeclampsia and its related cardiovascular diseases. Our results indicate that elevated HMGB1 expression and its release from hypoxic trophoblasts play a critical role in upregulating decorin while downregulating VEGF, contributing to the angiogenic imbalance in preeclampsia. A range of factors likely influences the preeclampsia-associated phenotype, and our findings could pave the way for further research into the potential therapeutic use of HMGB1 inhibition to manage preeclampsia or related cardiovascular complications.

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Ethical Approval

Animals were procured from the animal house, Jamia Hamdard, New Delhi after taking permission from the Institutional Animal Ethical Committee (IAEC; Protocol No.1689) of Jamia Hamdard, New Delhi, India. We follow the standards of the Committee for Control and Supervision of Experiments on Animals (CCSEA;173/GO/ReBi/S/2000/CCSEA), Government of India.

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Conflicts of Interest

We hereby declare that the manuscript has not been previously published in any language anywhere and that it is not under simultaneous consideration by another journal. None of the authors have any conflict of interest or any financial ties to disclose.

References

1. Yu H, Chen L, Du B. Necroptosis in the pathophysiology of preeclampsia. Cell Cycle. 2023;22(14-16):1713-1725.

2. Zakeri S, Rahimi Z, Jalilian N, Vaisi-Raygani A, Rezvani A, Dastafkan Z. Aberrant Methylation of the *SOD1* GENE, its Expression and Enzyme Activity in the Placenta of Patients with Preeclampsia. Rep Biochem Mol Biol. 2023;12(1):112-119.

3. Opichka MA, Rappelt MW, Gutterman DD, Grobe JL, McIntosh JJ. Vascular Dysfunction in Preeclampsia. Cells. 2021;10(11):3055.

4. Wang H, Zhang X, Liu C, Chen S, Liu X, Fan S. TAGLN2-Regulated Trophoblast Migration, Invasion and Fusion are Impaired in Preeclampsia. Front Cell Dev Biol. 2022;10:810633.

[DOI: 10.61186/rbmb.13.3.385]

5. Dimitriadis E, Rolnik DL, Zhou W, Estrada-Gutierrez G, Koga K, Francisco RPV, et al. Pre-eclampsia. Nat Rev Dis Primers. 2023;9(1):8.
6. Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. Am J Obstet Gynecol. 2022;226(2S):S1019-S1034.
7. Michalczyk M, Celewicz A, Celewicz M, Woźniakowska-Gondek P, Rzepka R. The Role of Inflammation in the Pathogenesis of Preeclampsia. Mediators Inflamm. 2020;2020:3864941.
8. Tomimatsu T, Mimura K, Endo M, Kumasawa K, Kimura T. Pathophysiology of preeclampsia: an angiogenic imbalance and long-lasting systemic vascular dysfunction. Hypertens Res. 2017;40(4):305-310.
9. Cornelis T, Odutayo A, Keunen J, Hladunewich M. The kidney in normal pregnancy and preeclampsia. Semin Nephrol. 2011;31(1):4-14.
10. Al-Kawaz HS, Yasser OM, Mousa MJ. A New Method to Estimate Inhibition Percentage of Endogenous Digitalis in Patients with Pre-eclampsia. Rep Biochem Mol Biol. 2022;11(1):138-145.
11. Chen DB, Zheng J. Regulation of placental angiogenesis. Microcirculation. 2014;21(1):15-25.
12. Jena MK, Sharma NR, Petitt M, Maulik D, Nayak NR. Pathogenesis of Preeclampsia and Therapeutic Approaches Targeting the Placenta. Biomolecules. 2020;10(6):953.
13. Lala PK, Nandi P. Mechanisms of trophoblast migration, endometrial angiogenesis in preeclampsia: The role of decorin. Cell Adh Migr. 2016;10(1-2):111-25.
14. Zhou Y, Gan G. The levels of peripheral blood TNF-α, Decorin and neutrophils MAPK1 mRNA levels of patients with preeclampsia and their clinical significance. J Matern Fetal Neonatal Med. 2023;36(1):2183745.
15. Ferrara N. Vascular endothelial growth factor. Arterioscler Thromb Vasc Biol. 2009;29(6):789-91.
16. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. Semin Nephrol. 2011;31(1):33-46.
17. Quasimi H, Naaz S, Dhyani N, Bhagat S, Ansari M. Evaluation of Hemodynamics and Oxidative Stress in the Pathophysiology of L-NAME Induced Preeclampsia in Rats. 2022;5(12):75–84.
18. Kuklina E V., Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the united states. Obstetrics and Gynecology. 2009;113(6):1299–306.
19. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. Semin Nephrol. 2011;31(1):33-46.
20. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation. 2011;123(24):2856-69.
21. Staff AC, Fjeldstad HE, Fosheim IK, Moe K, Turowski G, Johnsen GM, et al. Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. Am J Obstet Gynecol. 2022;226(2S):S895-S906.
22. Lala PK, Nandi P. Mechanisms of trophoblast migration, endometrial angiogenesis in preeclampsia: The role of decorin. Cell Adh Migr. 2016;10(1-2):111-25.
23. Khan GA, Girish GV, Lala N, Di Guglielmo GM, Lala PK. Decorin is a novel VEGFR-2-binding antagonist for the human extravillous trophoblast. Mol Endocrinol. 2011;25(8):1431-43.
24. Bdolah Y, Sukhatme VP, Karumanchi SA. Angiogenic imbalance in the pathophysiology of preeclampsia: newer insights. Semin Nephrol. 2004;24(6):548-56.
25. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2):e003497.

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