Research Article

Protective Role of Serum Amyloid P Component and Ceruloplasmin in Preeclampsia

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Abstract | Preeclampsia is a complex disorder affecting women's health. Although the pathophysiology of PE remains unclear, placental ischemia is widely regarded as a key factor. Timely detection and appropriate management are essential to avoiding serious complications for both mother and baby. The current study aimed to compare the plasma of preeclamptic females with controls using proteomic techniques. Blood samples from normotensive and preeclamptic women were analyzed using 2D-PAGE, and protein expression was compared using Image Master 2D-Platinum software. Statistical analysis and data visualization were performed using GraphPad Prism 5, with Student's *t*-test applied for analysis. Proteomic analysis revealed differential expression of two plasma proteins between preeclamptic and controls. Serum amyloid P-component (SAP) showed increased concentration by 1.12- and 1.1-fold in preeclamptic patients compared to controls, with a 1.0-fold increase in severe PE compared to mild PE. Similarly, ceruloplasmin (CP) exhibited a 3.04-fold increase in severe PE and a 1.44-fold increase in mild PE compared to controls, with a 2.1-fold elevation in severe PE relative to mild PE. Elevated SAP and CP levels in PE suggests a defensive response to inflammation, oxidative stress, endothelial dysfunction and ischemia, making them potential predictive biomarkers and therapeutic targets.

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Introduction

Preeclampsia is a common condition of pregnancy, marked by the onset of hypertension and proteinuria (English *et al*., 2015; Sibai *et al*., 2005). It is a leading cause of maternal mortality, responsible annually for over 50,000 maternal deaths worldwide (Karrar *et al*., 2024). According to WHO (2013), the likelihood of death due to pregnancy-related complications is 14 times higher in developing countries compared to developed ones.

Preeclampsia is a two-stage disease, beginning with defective placentation, followed by the release of pro-inflammatory factors from the affected placenta (Redman and Sargent, 2009). This triggers an in-

flammatory response, leading to altered expression of acute-phase proteins (Stubert *et al.*, 2016). These plasma proteins play a crucial role in restoring homeostasis (Steel and Whitehead, 1994).

These pro-inflammatory factors may further activate monocytes (Faas and de Vos, 2017). Activated monocytic cells and macrophages have also been shown to produce and secrete SAP and CP (Mazumder *et al.*, 1997; Xi *et al.*, 2015).

SAP, in particular, serves as an opsonizing protein and is involved in the resolution or repair phase of tissue injury (Haudek *et al.*, 2008; Pilling *et al.*, 2007; Pepys *et al.*, 1994; Familian *et al.*, 2007). This suggests that SAP may contribute to the regulatory mechanisms attempting to counterbalance inflammation in preeclampsia, though its exact role in disease progression remains to be fully elucidated.

Ceruloplasmin may increase by approximately 50 percent during inflammation (Steel and Whitehead, 1994). It is involved in host defense and repair processes during inflammation (Gitlin, 1988).

The objective of this study was to identify differentially regulated proteins in the plasma of preeclamptic patients. We identified differential expression of SAP and CP in the plasma of PE patients as compared to healthy controls. Their increased expression in PE suggests a compensatory response against placental ischemia, tissue injury and systemic inflammation.

Materials and Methods

Preeclampsia is characterized by the presence of elevated blood pressures (i.e., systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) and proteinuria after 20 weeks gestation.

Subjects with preeclampsia and normotensive pregnancies were selected from women attending the Obstetrics and Gynecology Department of different hospitals of Lahore. All participants provided informed consent before being enrolled in this study. Blood samples were obtained from normotensive pregnant women (n=20) and PE groups (n=10 severe and n=10 mild) between 29–40 weeks of gestation. Each blood sample was collected in vacutainer tubes containing EDTA. For separation of plasma, these tubes were centrifuged at 6000 rpm for 15 min, poured in labeled Eppendorf vials, and stored at −80°C. Total protein content of plasma samples was determined using the Bradford Protein Assay. After quantification, we performed 2-dimensional polyacrylamide gel electrophoresis (2D-PAGE) analysis.

Gel image analysis was carried out using the Image Master 2D-Platinum software. Plasma proteins were successfully identified by the Swiss 2D page database. Protein expressions were compared between PE groups and normotensive group.

Ethics statement

This study was conducted as part of a PhD research project submitted to the Department of Zoology, University of the Punjab, Lahore, Pakistan (2015). At the time of the study, formal ethical approval documentation was not routinely issued or is currently unavailable. Nevertheless, all procedures were carried out in accordance with the ethical principles and institutional guidelines applicable at that time.

Results

The use of two-dimensional gel electrophoresis and the following Image Master 2D Platinum Software analysis showed that the plasma levels of two proteins were differentially expressed between PE and normotensive controls. SAP and CP showing alterations in different stages of preeclampsia are presented in Table 1.

Serum amyloid P-component

Serum amyloid P-component showed up regulation by 1.12 and 1.1-fold in preeclamptic patient as compared to control. Its expression elevated 1.0-fold in severe PE compare to mild PE (Figure 1 and 2).

Table 1: *List of proteins altered in different stages of preclampsia*

Spot no.	Accession no.	Protein name	Function	Reference
1	P00450	Ceruloplasmin	Copper-containing iron transport protein with antioxidant ferroxidase properties	Guller *et al.*, 2008
15	P02743	Serum amyloid P component	Involved in innate immunity as well as acute-phase responses to inflammation.	Biro *et al.* 2007

Ceruloplasmin

Ceruloplasmin, in severe preeclampsia and mild preeclampsia, exhibited 3.04 and 1.44-fold up-regulation respectively as compared to control (C). Level of ceruloplasmin was enhanced 2.1-fold in severe PE as compared to Mild PE (Figure 3 and 4).

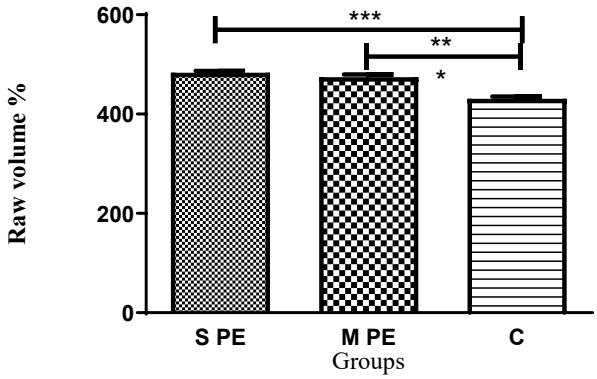

Figure 1: *Raw volume of Serum amyloid P-component in comparable groups. Values are Mean±SEM*
**** Significant at p<0. 01*

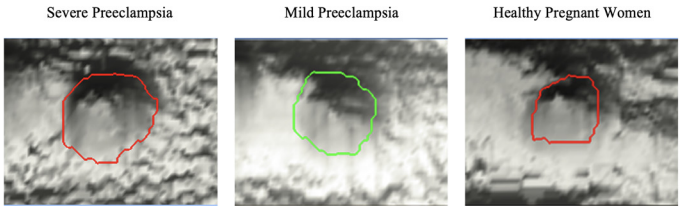

Figure 2: *Three-dimensional spot volumes of serum amyloid P-component.*

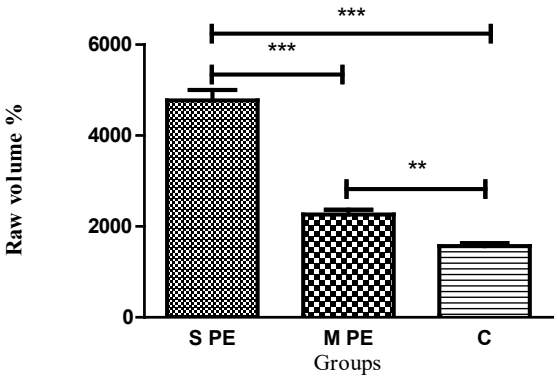

Figure 3: *Raw volume of ceruloplasmin in comparable groups. Values are Mean±SEM*
**** Significant at p<0. 01*

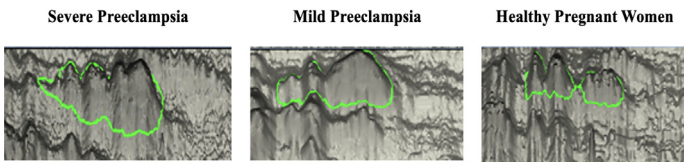

Figure 4: *Three-dimensional spot volumes of ceruloplasmin*

Discussion

Preeclampsia is a chronic hypertensive disorder marked by persistent high blood pressure and proteinuria, usually developing in the second trimester. (Aouache *et al.*, 2018). Oxidative stress of the placenta is considered to be a key intermediary step in the pathogenesis of preeclampsia (Hung and Burton, 2006). In response to this oxidative imbalance, the body may enhance the activity of antioxidant proteins as a compensatory mechanism to mitigate cellular damage and restore homeostasis (Krishna *et al.*, 2017).

This suggests that while oxidative stress plays a central role in disease progression, the upregulation of antioxidant defenses represents an attempt to counteract its harmful effects, potentially influencing disease severity and progression.

In this study, proteins whose concentrations were associated with preeclampsia included Serum amyloid P component (SAP), and Ceruloplasmin (CP). Serum amyloid P component (SAP), a glycoprotein, belongs to the pentraxin protein family and plays a role in innate immunity and acute-phase inflammatory responses. Typically, SAP is believed to be produced and secreted only in hepatocytes. However, in certain diseases, it can also be generated by macrophages and smooth muscle cells (Xi el al., 2015).

SAP was found to be upregulated in plasma of both mild and severe PE mothers in compared to normotensive control, with Atkinson *et al.* (2009) also reporting its over-expression in preeclamptic plasma relative to healthy pregnant women. Vascular endothelial dysfunction is considered a key abnormality in preeclampsia. Previous research suggests that endothelial dysfunction arise due to abnormal placentation, potentially resulting in placental ischemia. The ischemic placenta then releases bioactive circulating factors including pro-inflammatory cytokines that may contribute to maternal vascular endothelial damage (Roberts and Cooper, 2001; Dekker and Sibai, 1998; Reslan and Khalil, 2010).

Koenig (2007) reported association of elevated SAP with inflammation and ischemia. SAP facilitates the resolution of inflammation and mitigates fibrosis through several mechanisms (Pilling and Gomer, 2014).

Greater incidence of trophoblast apoptosis has been observed in preeclampsia (Straszewski-Chavez *et al.*, 2005). SAP serves as an opsonising protein, it attaches to apoptotic cells and other debris formed during inflammation, enhancing their clearance through phagocytosis (Murray *et al.*, 2011; Lu *et al.*, 2012).

Ceruloplasmin (CP), a ferroxidase enzyme, is crucial for regulating iron metabolism and redox reactions (Zhao *et al.*, 2018). It is synthesized in the liver containing 6 atoms of copper in its structure (O'Brien and Bruce, 2009). It is encoded by the CP gene (Royle *et al.*, 1987).

In the current study, ceruloplasmin showed an overall enhanced expression in mild and severe PE in comparison to control. Aksoy *et al.* (2003) reported that the plasma ceruloplasmin levels of the severe and mild preeclamptic groups was found to be upregulated compared with those of the healthy pregnant group.

Hypoxia later in pregnancy is often linked to complications such as preeclampsia and intrauterine growth restriction (Rytting and Audus, 2007). Hypoxia transactivate CP gene via hypoxia inducible factors-1 (HIF-1) activation and increases Cp mRNA transcription in hepatocytes (Mukhopadhyay *et al.*, 2000). Sarkar *et al.* (2003) and Guller *et al.* (2008) reported that under hypoxic conditions, concentration of ceruloplasmin and its ferroxidase activity is up-regulated. It inhibits the production of harmful oxygen compounds and shield cells from oxidative stress (Healy and Tipton *et al.*, 2007).

In preeclampsia, Ischemic placental tissue and destruction of RBC's due to vasospasm may be a source of toxic iron. Excess iron reacts with free radicals of cell membrane and lipoproteins tiggering lipid peroxidation, oxidative stress and endothelial cell injury (Serdar *et al.*, 2006). Ceruloplasmin converts toxic Fe2+ to less toxic Fe3+ because of its ferroxidatic activity, thus reduces oxidative damage to DNA and lipids (Hellman and Gitlin, 2002; Patel *et al.*, 2002).

The results of this study advocate that the upregulation of SAP and CP in preeclamptic patients represents a defensive response against oxidative stress, inflammation, and endothelial dysfunction linked with the disease. SAP, by promoting the clearance of apoptotic cells and inflammatory debris, may help lessen excessive inflammation and vascular injury. Similarly, CP, through its ferroxidase activity, plays a crucial role in reducing oxidative stress and preventing iron-induced cellular damage. These proteins appear to function as compensatory mechanisms aimed at restoring homeostasis in preeclamptic pregnancies. Further studies are required to explore their potential as predictive biomarkers or therapeutic targets for early diagnosis and management of preeclampsia.

Conclusions

We demonstrated that plasma serum amyloid p component and Ceruloplasmin concentrations were up-regulated in both mild and severe PE relative to normal pregnancy. This suggests that overexpression of these proteins activate a defense mechanism to counteract the effects of inflammation, hypoxia, apoptosis and ischemic placenta in preeclampsia. Serum amyloid p component and Ceruloplasmin may serve as potential predictive biomarkers for the progression of preeclampsia.

Author Contributions

Aasia Sharif was responsible for the conception and design of the study, collection of samples, execution of experimental work, data analysis, interpretation of results, and preparation of the manuscript draft. Nabila Roohi acted as the supervisor of the research project and provided critical intellectual input by revising the manuscript. Both authors reviewed and approved the final version of the manuscript.

Novelty Statement

This study provides novel insights by identifying previously unexplored biomarkers and their functional relevance in disease prediction.

Data access statement

The data generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Generative AI and AI assisted technology statement

The authors declare that no generative AI and AI

assisted technology was used in the creation of this manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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