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Is ischemia Modified Albumin is a Marker in Preeclampsia? A Case Control Study in Kolar Population-a South West of India

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ABSTRACT

Preeclampsia is a syndrome occurring in pregnancy that affects multiple systemic functions and leads to increased maternal and foetal morbidity as well as mortality. Ischemia Modified Albumin is a well-known marker of cardiac Ischemia. We aimed to test the hypothesis that variation in maternal serum Ischemia Modified Albumin (IMA) in preeclampsia during pre and post labour within 48 hours. A Longitudinal observational study was conducted between June 20 to April 2013in subjects with normal pregnancy (n=30), women with preeclampsia (n=30) and non-pregnant women (n=30) to evaluate the levels of IMA. The women studied were in 20-35thweeks of gestation visited obstetrics clinic in R.L. Jalappa hospital& Research center, Kolar, in a southern state of India. We estimated the maternal serum IMA levels before and after the delivery within 48 hours by using Albumin Cobalt Binding procedure. The results obtained were analysed by using Microsoft Excel 2013 and Quick R. p value < 0.05 is considered as statistically significant. The Median IMA level in the preeclampsia group before delivery 1.071ABSU [inter quartile range (IQR) 0.453-1.708ABSU] and the same within 48hrs after delivery 1.013ABSU [inter quartile range (IQR) 0.526-1.774 ABSU)] was significantly lower (p<0.02) than in normal pregnant group before delivery 0.328 ABSU [inter quartile range (IQR) 0.154-0.592 ABSU] and the same within 48hrs after delivery 0.570ABSU [inter quartile range (IQR) 0.060-0.751 ABSU. However, a significant increase in IMA concentrations (p<0.001) when compared to non-pregnant women 0.101 ABSU [inter quartile range (IQR) 0.049-0.358ABSU]. *In vivo* modification of albumin at the amino terminal residues loose in vitro Cobalt (Co (II)) binding ability. The trend of Modified albumin as IMA in preeclampsia shows the gradual increase after the delivery within 48 hrs. However the levels of IMA in normal pregnancy show a tenfold increase than the non-pregnant women.

Keywords: Ischemia Modified Albumin, Intrauterine Hypoxia, Preeclampsia.

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INTRODUCTION

Human developmental biology has been stirred by the emergence of evidence that the early placental environment is hypoxia[1]. In normal pregnancy intrauterine hypoxic environment, subsequent reperfusion and oxidative stress plays a crucial role in the pathophysiological trophoblast development illustrated by experimental evidences [2-4]. As a measurement of Cardiac ischemia in acute coronary syndromes, Ischemia Modified Albumin (IMA) is measured as a protein marker in several studies[5]. Studies reported with an evidence that during ischemia/ reperfusion, generation of highly reactive hydroxyl radical by reactive oxygen species (ROS) that results in site-specific modifications at N-terminus of the albumin moiety, especially at the N-Asp-Ala-His-Lys sequence, thereby producing IMA [6,7]. The aim of the present study was to determine the Cobalt, Co (II) binding ability to amino-acid residues at the N-terminus of human serum albumin in Maternal Serum of preeclampsia.

MATERIALS AND METHOD

Venous samples were collected from 30 preeclampsia women after confirming hypertension and proteinuria condition and 30 normal pregnant women with single tone pregnancies attending for routine checkup during at 20-35 weeks gestation and from 30 non-pregnant healthy women of reproductive age. In all cases, 5 ml of maternal blood sample was drawn in a vacutainer, allowed to clot and centrifuged at 3000Xg for 15 min to obtain the clear sera. The institutional ethical clearance and written consent forms from all the participants in the study were obtained. Women with known case history of diabetes Mellitus, connective tissue disease, cardiac disease, renal disease and history of recurrent miscarriage were excluded from the study. IMA was measured by the albumin cobalt binding test (ACB test). Serum samples collected from patients with preeclampsia before delivery and follow up of the same patient serum sample after the delivery within 48 hours were frozen at -80^0C within 30 minutes. Frozen samples were gently vortexes after thawing. As per the ACB test, 100µl of patient sample and 50 µl of cobalt chloride (Co (II)) are incubated for 5 minutes. During this incubation, the Co (II), which is a transitional metal that binds to the N-terminal residues of unaltered albumin in the sample; albumin for which the N-terminal residues is altered as a result of ischemic process binds to the Co (II) to a far lesser extent. 25µl of Dithiothreitol (DTT) forms a colored complex with Co (II) that is not bound to the modified N-terminal residues of albumin and this complex is measured at 470nm. The median interquartile range was used to express data and the Mann-Whitney, as appropriate to compare the groups. Two sided *p*-values are reported.

RESULTS AND DISCUSSION

Ischemia Modified Albumin (IMA) was measured in thirty normal pregnant and thirty preeclampsia women before and after the delivery within 48 hours. at a gestation age of 35 weeks that were compared to 30 non–pregnant women as controls. The Median IMA level in the preeclampsia group before delivery 1.0171 ABSU [inter quartile range (IQR) 0.453-1.708ABSU] and the same within 48hrs after delivery 1.013ABSU [inter quartile range (IQR) 0.526-1.774 ABSU)] was significantly higher (p<0.02) than in normal pregnant group before delivery 0.328 ABSU [inter quartile range (IQR) 0.154-0.592 ABSU] and the same within 48hrs after delivery 0.570ABSU [inter quartile range (IQR) 0.064-0.751ABSU]. But a significant lower (p<0.001) IMA concentrations when compared to non-pregnant women 0.101 ABSU [inter quartile range (IQR) 0.049-0.358ABSU] represents the 25th and 75th percentiles, together with the median, with whiskers showing the minimum and maximum serum IMA concentrations in Preeclampsia before and after the delivery, normal pregnant before and after the delivery and in non pregnant women expected under the hypothesis of neutrality with difference in the groups(Table 1 and Figure 1). Human serum Albumin sequence obtained from the database from NCBI in the FASTA format models, the structure is obtained using modular, marked the four amino acid residues N-Asp-Ala-His-Lys using Pymol visualization software tool. Since, characterization of these residues at N-terminal region binds to transition metal cations cobalt and nickel has been elucidated by HPLC, LC-MS and HNMR analysis [9] any modification to these residues produce defective albumin proteins that has the lower binding ability to cobalt metal ions, thus an insight of decreased Cobalt binding proposes a new assay for preeclampsia. Human serum albumin is a major, multi-functional glycoprotein with a single polypeptide chain consists of 585 amino acid residues (Figure 2). It consists of three structurally homologous, largely helical domains (I, II, and III), and each domain consists of two sub domains, A and B. The first four amino acids in the N-terminus is Asp-Ala-His-Lys acts as a specific binding site for transition metals such as cobalt (II), copper (II), and nickel (II). This portion serves as the most susceptible region for degradation compared to other regions of albumin[8]. Studies on the N-terminal binding of human Serum albumin with Co (2+) and Ni (2+) metals have been established by using various advanced techniques like, HPLC, LCMS, and NMR[9]. In ischemic condition, circulating albumin undergoes modification specifically at the amino terminus. This modified protein is termed as “ischemia modified albumin (IMA)” with the decreased binding ability to transition metals (Co (2+) and Ni (2+)). On the basis of this biochemical property, Bar-

Or et al. (1990) developed a rapid colorimetric assay method measuring using an inorganic compound cobalt chloride. Ischemia-induced alterations of the binding capacity of human serum albumin to exogenous cobalt are reported in disease state. The possible in vivo modification to human serum albumin (HSA) includes glycation and oxidation. However, a significant increase in IMA was observed under various pathological conditions such as diabetes, myocardial infraction, etc., is due to the enormous generation of free Radical species under Oxidative stress condition[10]. Thus, generated IMA can be utilized as a protein oxidant marker in the preeclampsia condition. The present study evinced the variation in IMA level in non-pregnant (group 1), and normal pregnant before and after delivery (group 2) and preeclampsia before and after delivery (group 3). According to Ustun Y and his co-workers, IMA levels were significantly higher in the mild and severe preeclampsia groups than in the control group[11]. IMA appear to be significantly increased during pathological pregnancies and thus IMA could be used as a biological marker of preeclampsia[12]. The similar observation also obtained in our study with raised IMA levels in Preeclampsia before delivery and after the delivery within 48 hours. A study conducted on IMA in preeclampsia[13] stated that serum IMA level as a marker of myocardial ischemia; preeclampsia found that there is no significant relationship between IMA levels and preeclampsia, in women with or without small-for-gestation-age (SGA). Contradictory to this observation, in the present study, we found that there is a marked increase in the IMA levels in normal pregnancy and before and after delivery within 48 hours, Compared to non-pregnant group. Even though, further studies are necessary to evaluate the IMA levels at different intervals during pregnancy and after delivery with increased sample size.

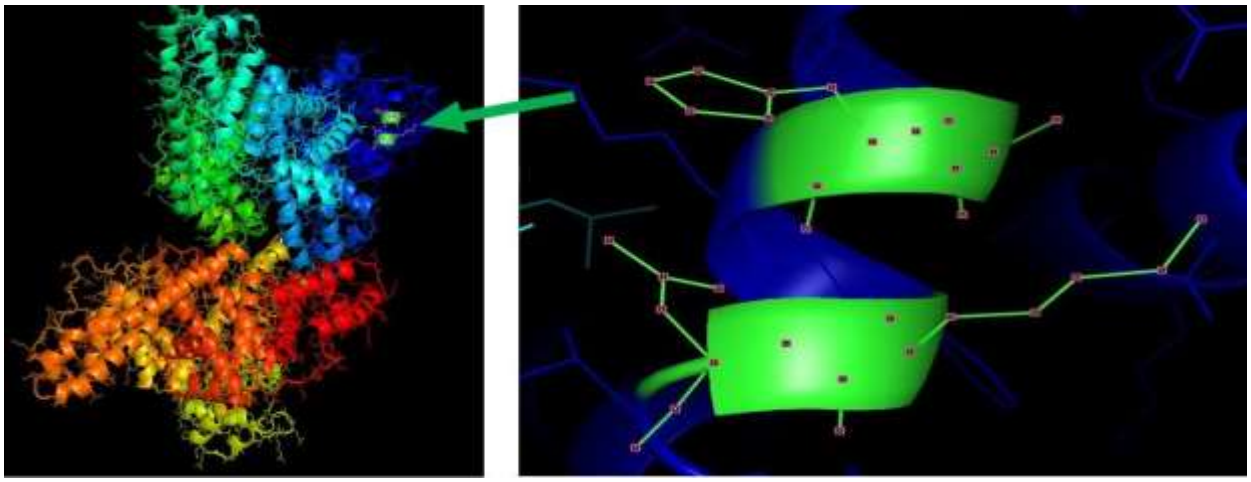

Figure 2: Structure obtained using modular, marked with the four amino acid residues N-Asp-Ala-His-Lys using Pymol visualization software tool

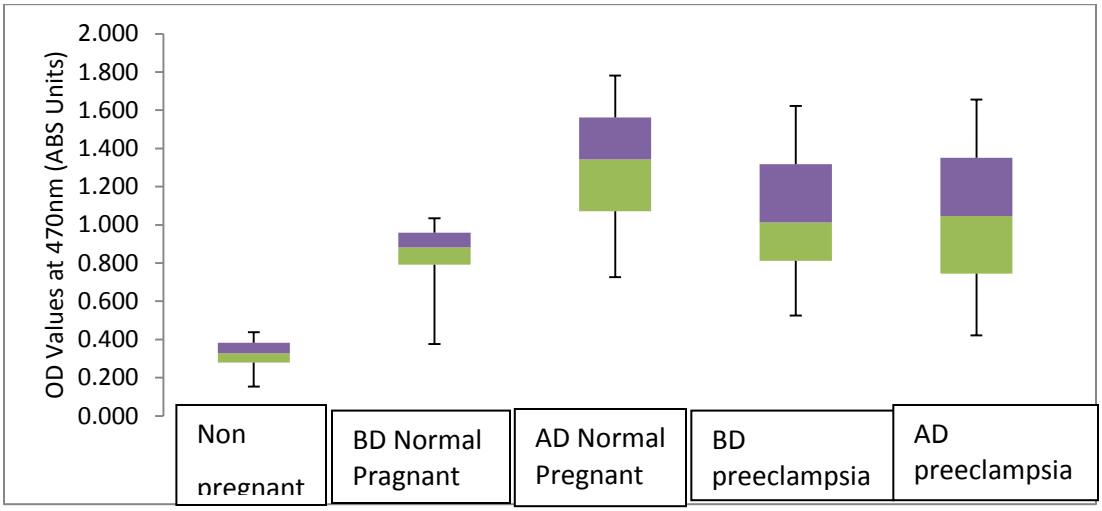

Figure 1: Box plot showing the 25th and 75th percentiles, together with the median, with whiskers showing the minimum and maximum IMA maternal serum concentrations in Preeclampsia before and after the delivery within 48hrs, normal pregnant before and after the delivery within 48hrs., and in non –pregnant women expected under the hypothesis of neutrality with difference in the groups.

Table 1: IMA values in normal pregnancy and preeclampsia before and after delivery

Sl.no	Non pregnant woman	IMA value in normal pregnant woman		IMA value in preeclampsia pregnant woman	
		Before delivery	After delivery	Before delivery	After delivery
ABSU	0.101	0.328	0.570	1.071	1.013
I.Q.R	0.049-0.358	0.154-0.592	0.064-0.751	0.453-1.708	0.526-1.774

CONCLUSION

An *in vivo* modification of albumin at the amino terminal residues loose *in vitro* ligand Cobalt Co(II) binding ability. The trend of Modified albumin as IMA in preeclampsia shows the gradual increase before the delivery. However, the levels of IMA in non-pregnancy shows 3.2- 10 fold decrease than the normal pregnant women and preeclampsia group. Increased IMA concentrations in preeclampsia before and after delivery and that was evaluated in terms of cobalt binding to specific amino acid in albumin.

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