

Serum ischemia modified albumin as a potent biochemical marker in pre-eclampsia patients attending a tertiary care hospital in central India

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Abstract

Introduction: Pre-eclampsia (PE) a pregnancy specific disease, the most common cause of fetal and maternal death yet, no specific prevention and treatment is available. Reliable biochemical markers for prediction and diagnosis of PE can have a better impact on maternal health and several of these markers have been suggested till now. Recently Ischemia Modified Albumin (IMA) has emerged as a marker in different diseases, where ischemia is the origin or consequence behind disease pathology.

Materials and Methods: 30 patients with PE were selected for the study and compared with 30 pregnant healthy controls. IMA IMA/albumin with other routine biochemical markers was estimated in these patients.

The results were then statistically analysed.

Results: IMA levels were found significantly raised in PE patients as compared to normal pregnant controls (p value<0.001) A significant correlation was also found between IMA levels and MDA levels in PE ($r=+0.3$ p value<0.05).

Conclusion: IMA generated by hypoxia/ischemia driven oxidative stress is also raised in PE, hence can be used as a biomarker in PE. Further studies are needed to establish the relationship between IMA, disease process and its association with severity of the disease.

Keywords: Pre-eclampsia, Ischemia Modified albumin.

Introduction

Pre-eclampsia has long been known to be a multisystem disorder of unknown aetiology. It has been found to be characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after the 20th week in a previously normotensive and non-proteinuric women.¹

The pathogenesis of the disease is due to impaired endovascular invasion of cytotrophoblast into the spiral arteries. Over the years several theories such as; increased insulin resistance, oxidative stress, immunological tolerance between maternal and fetal tissue etc have been put forward.²

Pre-eclampsia is one of the most common causes of prematurity. It accounts for 25% of all very low birth weight infants with birth weight less than 1500 grams. Pre eclampsia has a recurrence risk of 32% and a recurrence risk of 46% has been found in the case of for pre-eclampsia superimposed on pre-existing chronic hypertension.^{3,4}

Hypertensive disorders of pregnancy were classified by working group of National High Blood Pressure Education Programme (NHBPEP 2000) into five types :-

a. Gestational Hypertension

1. Elevation of blood pressure $\geq 140/90$ mm Hg noted for the first time during pregnancy after 20 weeks of gestation.
2. No proteinuria.

b. Pre-eclampsia

1. Elevation of blood pressure $\geq 140/90$ mm of Hg noted for the first time during pregnancy after 20 weeks of gestation.

2. Proteinuria of ≥ 300 mg/24 hours by dipstick method in a random urine sample.

c. Eclampsia

1. Eclampsia is defined as the development of seizures that cannot be attributed to other causes in women with pre-eclampsia.

d. Pre-eclampsia superimposed on chronic hypertension

2. New onset of proteinuria ≥ 300 mg/24 hours in hypertensive women but no proteinuria before 20 weeks of gestation.

e. Chronic hypertension

3. It is defined as the presence of BP $\geq 140/90$ mm Hg before pregnancy or diagnosed before 20 weeks gestation or hypertension first diagnosed after 20 weeks gestation and persisted after 12 weeks postpartum.^{5,6}

Defective endovascular trophoblast invasion and inadequate remodelling of uterine spiral arteries has been considered the causative factor. This defective invasion leads to hypoxic intrauterine environment which in turn leads to generation of oxidative free radicals. Accumulation of biomarkers of oxidative stress accompanied by depletion of antioxidant reserves is considered as a hallmark of pre-eclampsia.^{7,8}

As placental hypoxic conditions are found in pre-eclampsia and oxidative stress is implicated in its pathogenesis maternal serum Ischemia Modified Albumin (IMA) can be a potent biomarker of pre-eclampsia.

Transition metals bind to the amino terminal of Human Serum Albumin (HSA) under physiological conditions. Ischemia reperfusion injury generates reactive oxygen species which in turn modifies the N-terminal region of HSA. This modification in HSA, reduces its capacity to bind to the transition metals. This chemically changed albumin is called as ischemia modified albumin.^{9,10}

Objectives

To determine and compare the values of IMA in pre-eclamptic primigravida and healthy pregnant females.

Materials and Methods

This cross sectional study was conducted in women with gestational hypertension and pre-eclampsia who were assigned as cases. Healthy pregnant females were considered as controls. The study was conducted from April 2017 to April 2018 in Shankracharya Hospital, Bhilai C.G.

The cases and controls were selected from tertiary care hospitals in local geographical area.

Written informed consent was taken from each study subject.

I Selection of study subjects

1. Based on inclusion and exclusion criteria total 60 study subjects (30 cases and 30 controls) were selected for the study. A proforma was used to record relevant information and patient's data.
2. Cases= 30 women with hypertensive disorders of pregnancy were selected on the basis of definition given by National High Blood Pressure Education Programme (NHBPEP 2000).
3. Controls =30 healthy pregnant females.

Inclusion Criteria

1. 30 diagnosed cases of pre-eclampsia in the age group of 20-45 years.
2. Pregnant females of ≥ 20 weeks of gestation with blood pressure of $\geq 140/90$ mm of Hg noted first time during pregnancy on ≥ 2 occasions at least 6 hours apart with proteinuria of $\geq 1+$ by dipstick method in a random urine sample was considered to have pre-eclampsia.
3. Control = healthy sex matched 30 controls were taken

Exclusion Criteria

1. History of chronic hypertension that was present before pregnancy.
2. History of diabetes mellitus and/or who are on insulin therapy.
3. Subjects taking anti-hypertensive drugs.
4. Liver disease patients.

Collection of Blood samples

1. About 3ml of blood was drawn under aseptic precautions from selected subjects, after overnight fasting of 12 hours.
2. Blood was collected in plain vial for serum IMA (maternal).

3. The blood samples were centrifuged at 3000 rpm for 10 minutes to obtain the serum.

Parameters to be Measured

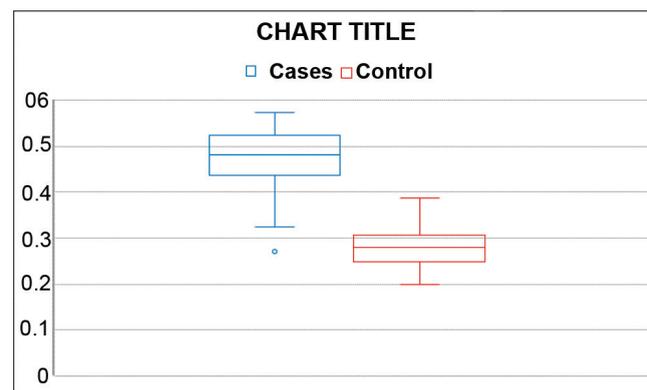
1. The parameters which are to be measured in the cases and controls is maternal serum IMA.

Measurement of serum ischemia modified albumin

It is done according to Bar Or et al 2000. Known amount of cobalt was added to the serum sample and unbounded cobalt was measured by the intensity of coloured complex formed after reacting with dithiothreitol by spectrophotometer at 470 nm.¹¹

Results

Parameter	Case	Control	P – value
Age	27.7 \pm 4.99	26.93 \pm 4.55	0.5367
IMA	0.468 \pm 0.075	0.279 \pm 0.047	< 0.0001*
*significant difference			



The mean value of IMA was 0.468 ± 0.075 in the cases and control it was 0.279 ± 0.047 .

The IMA variables were noted on cases as well as control. All the variables are continuous in nature. T-test for two independent samples has been applied to data as the samples are independent. It has been observed that cases and controls were matched for age and there was no significant difference found in age of cases and control. IMA levels were found to be higher in cases compared to control. The difference of total bilirubin turned out to be highly significant statistically. This type of graph is used to show the shape of the distribution, its central value, and its variability. In a box and whisker plot, the ends of the box are the upper and lower quartiles, so the box spans the interquartile range.

Discussion

Pre-eclampsia is associated with defective placentation leading to failure of conversion of small diameter high resistance vessels to large diameter low resistance vessels leading to ischemic reperfusion injury leading oxidative stress and generation of free radicals.¹¹⁻¹² Eclampsia is the end stage of the disease characterized by generalized seizures. 2%-8% of pregnancies are complicated by the onset of Pre eclampsia

and Eclampsia. Approximately 10%-15% of direct maternal deaths are associated with these conditions.^{12,13}

Serum IMA has been observed to be significantly increased in diseases where oxidative stress is the consequence of the disease process. In the present study a significant rise in serum IMA was seen in pre-eclamptic women compared to normal pregnant women. pregnancy is associated with haemodilution leading to decrease in plasma albumin concentration. Hence IMA was normalized to albumin by calculating IMA/Albumin ratio. The observations from this study were in accordance with the studies done by GafSou et al¹⁵ and Yusuf Ustun et al.¹⁶ Generation of free radicals causes alteration of NH₂ terminus of Human Serum Albumin which leads to reduced binding of albumin to cobalt as compared to normal healthy pregnant women.¹⁴

However in a limited study done by Van Rijn et al serum IMA was found elevated in normal pregnant controls compared to the non-pregnant controls ($p=0.015$) but the IMA levels in pre-eclampsia were similar to those of normal pregnant controls ($p=0.65$). The discrepancy in these studies could possibly be explained by smaller number of patients and differences in severity of pre-eclampsia.¹⁵⁻¹⁷

Our study showed a significant increase in serum MDA in parallel to the observations of Ebru Dikensoy et al,¹⁸ Yoneyama Y et al¹⁹ and Mohd. Sahail et al.²⁰ These findings on significantly increased maternal serum MDA provides further evidence that inappropriate or excessive lipid peroxidation may play an important role in pathophysiology of pre-eclampsia. There is significant positive correlation between the maternal serum IMA and MDA as well as serum IMA/ALB and MDA in pre-eclampsia. These correlations suggest that there occurs increase in serum IMA and IMA/ALB with increase in oxidative stress due to ischemia. This is in accordance with the work of Debasis Roy et al²¹ who suggested that increased IMA levels may result from increased oxidative stress irrespective of whether caused by ischemia reperfusion injury or other mechanisms which can be a result of primary reduction in blood flow.

Conclusion

IMA normalized to albumin appears to be significantly increased in PE. This suggests that measurement of this oxidative biomarker may be useful in monitoring pregnancies with respect to the development of pre-eclampsia.

Implications

IMA can be very useful in monitoring pregnancies with respect to the development of pre-eclampsia. It shall be very useful in near future to compare and elucidate proper diagnosis of pre-eclampsia followed by its treatment.

Conflict of Interest: None.

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