DOI: NJLM/2014/10454:2017

Original Article

Biochemistry Section

Is Nonprotein Nitrogenous Compounds Have Role in Preeclampsia

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ABSTRACT

Introduction: Preeclampsia is a pregnancy-specific disorder, which is life-threatening, both to foetus as well as mother. It may lead to early onset of CVD risk and stroke. Chronic kidney disorders may also lead to preeclampsia. Non protein nitrogenous substances urea, uric acid, creatinine are considered to have role in preeclampsia and determination of these markers during pregnancy is important to diagnose kidney function especially at women with preeclampsia signs.

Materials and Methods: Thirty women diagnosed to have preeclampsia and thirty women (age matched) with normal pregnancy were taken as controls. Blood pressure measurements were done by using a sphygmomanometer and biochemical parameters like serum urea, uric acid, and creatinine were measured by using commercial kits. Statistical analysis were done by unpaired t- test.

Results: A significant increase of SBP, DBP, Uric acid and Urea levels ($P<0.05$) have been seen in woman with preeclampsia compared to normal pregnancy but, the levels of creatinine doesn't show any significant differences between two groups.

Conclusion: Creatinine, urea and uric acid are non-protein nitrogenous metabolites that are cleared from the body by the kidney through glomerular filtration and also used as indicators of kidney function and other conditions. Determination of these parameters in serum during pregnancy helps to diagnose kidney function especially at women with preeclampsia signs. In the present study it was showed that uric acid might be having a role in preeclampsia even though urea levels were elevated. It was found of little value and creatinine had no predictive value in preeclampsia. Further studies with large samples were needed in order to get a clear clinical picture of these parameters in the issue of preeclampsia.

Keywords: Antiendothelial factors, Glomerular endotheliosis, Non protein nitrogenous substances, Pre-eclampsia

INTRODUCTION

Preeclampsia is a pregnancy-specific, multisystem disorder that is characterized by the development of hypertension and proteinuria after 20 weeks of gestation [1]. Preeclampsia increases perinatal mortality 5-fold and kills 50,000 women yearly worldwide [2]. The disorder complicates approximately 5 to 7 percent of pregnancies, if left untreated it can develop into eclampsia, the life-threatening occurrence of seizures during pregnancy. Complications of hypertension are the third leading cause of pregnancy-related deaths, superseded only by hemorrhage and embolism. Preeclampsia is associated with increased risks of placental abruption, acute renal failure, cerebrovascular and cardiovascular complications, disseminated intravascular coagulation, and maternal death. Consequently, early diagnosis of preeclampsia and close observation are imperative [3].

Preeclampsia may be life-threatening for both foetus and maternal increasing morbidity and mortality [4]. In the mother, preeclampsia may cause premature CVD, such as chronic hypertension, ischemia heart disease, and stroke, in later life, while children born after preeclamptic pregnancies and who are relatively small at birth, and have an increased risk of stroke, coronary heart disease, and metabolic syndrome in adult life. The sole curative treatment being delivery, management must continuously balance the risk-benefit ratio of induced preterm delivery and maternal- fetal complications. Screening women at high risk and preventing recurrences are also key issues in the management of preeclampsia [5,6].

Chronic kidney disease (CKD) is a risk factor for pre-eclampsia, which may unmask underlying renal pathologies [7]. Prospects for women with moderate to severe CKD are grave, with 15% progressing to end-stage renal disease within 1 year and 90% having a problematic pregnancy [8]. Creatinine, urea and uric acid are non-protein nitrogenous metabolites that are cleared from the body by the kidney following glomerular filtration. Therefore, their determination in serum during pregnancy is of a major importance to diagnose kidney function especially at women with preeclampsia signs.

Hyperuricemia, higher circulating uric acid concentration, present in 75% of preeclamptic women, has long been attributed to altered renal function and considered a marker of disease severity [9]. Furthermore, uric acid has intracellular signaling roles capable of initiating inflammatory and redox cascades [10,11]. And recently, it was identified that uric

Parameters	Group-A (preeclampsia) Mean ± SD	Group-B (normal pregnancy) Mean ± SD	p value
Systolic blood pressure (mm of Hg)	175.30±8.56	116.7±5.66	0.001*
Diastolic blood pressure (mm of Hg)	104.76±5.89	75.44±5.27	0.001*
Serum Uric Acid (mg/dl)	5.14±0.39	3.52±0.18	0.004*
Serum Urea (mg/dl)	17.75±3.05	13.0±0.98	0.03
Serum reatinine (mg/dl)	0.79±0.06	0.72±0.02	0.39

[Table/Fig-1]: Shows the values of NPN substances in preeclampsia and normal pregnancy both uric acid and urea levels were significantly elevated in preeclampsia but the levels of creatinine doesn't show any significant differences between two groups

acid have role in vascular damage and in oxidative stress so, evoked as a contributor to the pathogenesis of preeclampsia [12,13]. Uric acid role in glomerular endotheliosis the renal lesion which are caused by circulating antiendothelial factors such as soluble fms-like tyrosine kinase-1, induce endothelial dysfunction and the accompanying symptoms. Moreover, afferent arteriolar disease often seen in preeclampsia and would be consistent with a uric acid–mediated effect. This concept may explain why patients with preeclampsia have an increased likelihood of developing hypertension [14,15]. Urate retention, explained by Circulatory changes in the kidney that is Angiotensin II is known to depress urate clearance without lowering GFR although this may not be the cause of intense vasoconstriction in preeclampsia [16]. Preeclamptic uraemia is ischaemic in origin. Arterial constriction, glomerular endothelial swelling and intravascular fibrin deposition are all developed sufficiently to explain the deterioration in renal function [17]. Most evidence suggests that decreased renal clearance is the most important mechanism. But, the exact cause of hyperuricemia in preeclampsia has not been established definitively

Urea which is the catabolic product of ammonia and an important marker to assess the kidney functions seems to be raised in preeclampsia. This can be explained with the occurrence of microangiopathic haemolysis, which is related to the injury of endothelium in the group with pre- eclampsia changes. As a consequence, urea synthesis in liver would be increased as well as the incapability of kidneys to excrete urea from blood with such a high concentration may explain to some extent about urea [18].

Creatinine which is another important marker to assess kidney functions had role in preeclampsia remain controversial. Few studies observe insignificant change in creatinine levels [19, 20]. On the other hand, an early study showed increased creatinine level but said that it was of no predictive value in preeclampsia [21].

With this background we have investigated the role of these non-protein nitrogenous substances which are the markers of renal functions in normal pregnancy and preeclampsia.

MATERIAL AND METHODS

This study is a cross-sectional case control study done in Department of Biochemistry Bidar Institute of Medical Sciences Bidar (Karnataka), India. After informed consent, thirty women diagnosed to have preeclampsia defined as BP greater than 140/90 mm of Hg and proteinuria of 300mg or greater on minimum two occasions and thirty women (age matched) with normal pregnancy were taken as controls. The exclusion criteria for patients was already hypertensive before 20 weeks of gestation or suffering from diabetes, asthma, heart disease, kidney disorders, liver disorders auto immune disorder, twin pregnancy, molar pregnancy or eclampsia or on such medications that may alter the diagnosis of true preeclampsia. Blood pressure measurements were done by using a sphygmomanometer and proteinuria analysis was performed using standard procedures.

Sampling: 3 ml of blood from the cubital vein was collected in a plain bottle. Serum was separated from the blood samples by centrifuged at 2000 rpm for 15 min.

Biochemical Analysis: Serum uric acid, Serum urea and creatinine levels were measured by using commercial kits. Analysis of parameters was done on Beckman CX9 auto analyzer.

Statistical Analysis: The statistical Package for the Social Sciences (SPSS version 11.5 for Windows) was used for statistical analysis. Results were expressed as mean ± SD. Unpaired t-test (one tailed) was used to compare the means, and a P value less than0.05 was considered to be statistically significant.

RESULT [Table/Fig-1]

DISCUSSION

It is well known that preeclampsia, a hypertensive disorder during pregnancy, is one of the most potential complication contributing to preterm labour, perinatal mortality, maternal mortality, intra uterine growth retardation, low birth weight infants and many such related problems. So, this study was attempted to understand the role of non protein nitrogenous substances so called renal markers uric acid, urea, and creatinine in preeclampsia. In the present study we noted significant increase of Systolic blood pressure, Diastolic blood pressure in preeclampsia and we also observed abnormal elevated levels of uric acid, and urea in preeclampsia but the levels of creatinine had not shown any difference in both the groups.

Whether the elevated levels of Uric acid can be taken as a predictive indicator for the Preeclamptic disorder remains to be considered. While there are majority of studies which shows significantly elevated levels of Uric acid in preeclampsia

[22, 23], but there are also few studies which find no such clear cut significance in the respective results.

Uric acid the end product of purine metabolism synthesis may be increased because of death and damage of trophoblastic cells in proliferation or by increased reabsorption and decreased excretion of uric acid and physiologic response to hypovolemia, [24, 25] or may be due to increased production from maternal, fetal or placental tissues breakdown and may be due to increased xanthine oxidase (XO) activity but, the reason behind increased XO activity in preeclamptic women are unclear [26]. Uric acid concentrations are influenced by diet, alcohol consumption, increased cell turnover, enzymatic defects in purine metabolism or altered kidney function [27]. Uric acid posses antioxidant free radical scavenging property which may also oppose harmful effects of oxidative stress but, in preeclampsia the uric acid is transformed into free urate radical, and it cannot be recycled back to its anti-oxidant state because of reduced ascorbate availability, and starts potentially oxidatively modifying placental proteins and lipids in preeclampsia [28, 29]. Hyperuricemia which is related to oxidative stress and formation of reactive oxygen species (ROS) may reflect impaired endothelial integrity, in which endothelial dependent vascular relaxation produced by nitric acid (NO) is reduced which predicts cardiovascular and renal dysfunction, and oxidative stress of the placenta may be considered to be the major step contributing in the pathogenesis of preeclampsia [25]. Bainbridge and Roberts et al., [26] proposed that the placental vasculature entirely relay on vasoactive compounds produced or circulating substances like endothelial derived NO for hemodynamic control and for the maintenance of optimized placental perfusion. In preeclampsia Hyperuricemia decreases the NO availability which would compromise to placental perfusion, and could inhibit fetal growth [30, 31]. Uric acid also has inflammatory action mediation of pro-inflammatory cytokines Gulati R et al., observed that Preeclamptic women have increased concentration of circulating TNF-α which was positively correlated to circulating uric acid concentrations [32, 33]. The increased frequency of preterm birth and growth restriction was present in hypertensive women with elevated concentration of uric acid even in the absence of proteinuria [26].

These evidences suggest that elevated levels of uric acid even in absence of proteinuria can be considered as a risk factor for developing preeclampsia. Eventhough the pathological role of uric acid in preeclampsia had explained to certain extent there are studies which inferred that uric acid is not a consistent predictive factor for the development of preeclampsia [34]. This parameter may have little value in the prediction of preeclampsia but it may often correlate with disease severity.

In our study we observed elevated urea levels in preeclampsia but not significant, the observations are in line with few studies [18, 35] who also observed small change in two groups but not significant. The possible explanation is excretion of urea is dependent on Renal Blood Flow (RBF) and is the result of glomerular filtration, but less tubular reabsorption. The urea reabsorption takes place in proximal tubule and the inner medulary collecting duct. Hypovolemia which leads to high angiotensin II and an angiotensin II hypersensitive state such as pre-eclampsia, efferent arteriolar resistance and filtration is increased. This process allows normal glomerular filtration fraction when RBF is decreased. The increased filtration fraction leads rise in protein concentration and oncotic pressure within the efferent arteriole, enhancing fluid reabsorption from the proximal tubule along with Urea transport which follows water reabsorption. So, Angiotensin II promotes direct tubular reabsorption of water, and in turn, urea may be the reason for elevated levels observed in preeclamptics [35-37].

The study observes insignificant changes in levels of creatinine in both groups. The study stands in line with studies of Mohamed Abdulfatah Abdulmunem et al., and Salako BL et al., [19, 20] who also observed insignificant change in creatinine level in two groups. Egwuatu et al., [21] showed increased creatinine level but proposed that it is of no predictive value in preeclampsia.

The differences in the levels of urea and creatinine observed between the two groups were not statistically significant indicating that these parameters are of little value in the prediction of preeclampsia.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Publishing: **Sep 01, 2014**