RESEARCH ARTICLE

ASSOCIATION OF TNF–α AND URIC ACID IN WOMEN WITH PRE-ECLAMPSIA

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DOI: 10.5455/ijmsph.2013.220820131 **Received Date: 04.04.2013** **Accepted Date: 22.08.2013**

ABSTRACT

Background: TNF – α, a cytokine of a generalized intravascular inflammatory reaction, has been also shown to cause microvascular protein leakage and hypertrygliceridemia which are associated with pre-eclampsia. Increased serum uric acid is also associated with hypertension.

Aims & Objective: To study the relationship between Tumour Necrosis Factor – alpha (TNF – α) with uric acid and to access the role of TNF – α as a determinant of Pre-eclampsia in women.

Material and Methods: 100 patients with pre-eclampsia were studied out of which 50 were mild and 50 were severe pre-eclamptics. They were compared with 50 healthy subjects. Subjects were of similar gestational age, body mass index (BMI) and parity matched. They were all primigravidas at third trimester of pregnancy.

Results: All studied subjects belonged to age group 28-40 years. The difference in mean age of healthy subjects and pre-eclamptics was non-significant (P=0.8). BMI values were ranged from 18-43 kg/m^2. No significant difference was observed between healthy pregnant women and pre-eclamptics. Serum TNF – α co-related significantly with Mean Arterial Pressure (MAP) and Uric acid levels. The association of TNF – α with uric acid was considerably significant compared to its association with other variables. The result showed that TNF – α is a strong determinant of pre-eclampsia.

Conclusion: A co-relation exists between TNF – α and uric acid. The observed co-relation indicates that monitoring TNF – α and uric acid levels in Pre-eclamptic women might serve to help prevent the development of pre-eclampsia in pregnant women.

Key-Words: Pre-Eclampsia; TNF – α; Mean Arterial Pressure

Introduction

Pre-eclampsia is a complication of pregnancy constituting a major cause of maternal morbidity and mortality worldwide. The cardinal clinical features of the condition are hypertension, edema and proteinuria occurring after 20 weeks of gestation in women who were not previously known to be hypertensive.[1]

Hypertension was defined as 140 mmHg systolic and 90 mmHg diastolic blood pressure, when measured on 2 consecutive occasions at least 24 hrs. apart.[2] A clinical diagnosis of pre-eclampsia includes proteinuria (300 mg or more of urinary protein during 24 hrs period) and edema (swelling of hand and feet) arising in the second half of the pregnancy in a previously normotensive women.[3] Importantly, the pregnancy induced hypertension was differentiated into two subgroups (mild and severe).[4]

An immunological disturbance causes abnormal placental implantation resulting in decreased placental perfusion. This abnormal placental perfusion stimulates the production of substances in the blood that activate, injure the endothelial cells.[5] Pre-eclampsia is thought to be caused by shallowly implanted placenta which becomes hypoxic, leading to an immune reaction characterized by secretion of up regulated inflammatory mediators from the placenta and acting on the vascular endothelium.[6]

TNF – α which is a suggestive cytokine of a generalized intravascular inflammatory reaction.[7] It is derived from the macrophages, lymphocytes, vascular endothelial cells, trophoblasts in the placenta. It induces functional

alteration in endothelial cells.[8] It has been also shown to cause microvascular protein leakage and hypertrygliceridemia which are associated with pre-eclampsia.[9]

Increased serum uric acid is associated with hypertension. In pre-eclampsia, the epithelial lining of glomerulus may be damaged due to high blood pressure and formation of blood clot. This may lead to decrease in the renal tubular excretion. The decreased tubular excretion or placental tissue breakdown may be responsible for increase in uric acid level in patient with pre-eclampsia.[10]

Further, an attempt has been made to evaluate the relation of these contributing factors with each other and significance of their association in pre-eclamptic subjects.

Materials and Methods

The study was conducted from 2009-2011 at Mahila Chikitsalaya Jawahar Lal Nehru Medical College and associated group of hospitals, Ajmer. A total of pre-eclamptic women were enrolled for this study out of these 50 subjects were mild pre-eclamptic and 50 were severe. The results were compared with 50 age and parity matched healthy pregnant women. All subjects were primigravidas and their gestational age were ranging from 28-40 weeks.

Mild pre-eclampsia defined by the American College of Obstetrics and Gynecology (ACOG; 2002) criteria as: (1) Blood pressure > 140/90 mmHg for two readings 6 hours apart; (2) Proteinuria > 300 mg/24 hours or +1 dipstick; (3) Edema.

Severe pre-eclampsia defined by American College of Obstetrics and Gynecology (ACOG; 2002) criteria as: (1) Blood pressure > 160/110 mmHg for two readings 6 hours apart; (2) Proteinuria > 5 gm/24 hours or +2, +3 dipstick; (3) Serum creatinine > 1.2 mg/dl; (4) Platelets < 100,000/mm^3; (5) Microangiopathic hemolysis; (6) Elevated liver enzymes; (7) Epigastric pain or right quadrant pain; (8) Persistent headache or other cerebral or visual disturbances; (9) Intrauterine growth restriction (IUGR); (10) Pulmonary edema; (11) Oliguria.

Exclusion criteria were Multiple pregnancy, Chronic hypertension, Premature rupture of membranes or clinical chorioamnionitis, Symptomatic inflammatory diseases, Diabetes Mellitus and Chronic renal disease.

The local ethics committee approved the study. Verbal consent has been taken from patients after explaining the aim of the study.

Anthropometric Measurements: Height and weight were measured and BMI was calculated as kg/m^2.

Biochemical Measurements: Human TNF –α concentration were measured by Sandwitch Elisa method.[11] Serum Uric acid concentrations were measured by Uricase, Trinder, end point assay.[12]

Mean arterial Blood pressure was determined by using the equation = (2 x diastolic + systolic) / 3 mmHg.

Statistical Analysis: Data are expressed as mean ± standard deviation. The means were compared using student's t- test. Pearson's correlation analysis was used for correlation of parameters measured. Analysis was two tailed and a p value ≤ 0.05 was considered statistically significant.

Results

The anthropometric and biochemical characteristics of the subjects are reported in the table. The mean gestational age of healthy pregnant, mild pre-eclamptics and severe pre-eclamptics was 33.60 years, 34.28 years and 33.76 years respectively with age range from 28 to 40 years. The difference in mean gestational age of controls, mild and severe pre-eclamptics was non-significant (p=0.4, p=0.7, p=0.3) table - 2.

Values of BMI in all subjects ranged from 18-43 kg/m2 (mean ± standard deviation → 29.68 ± 5.41 kg/m^2, 30.08 ± 6.65 kg/m^2 and 29.88 ± 6.08 kg/m^2 respectively, table -1). These values did not show significant difference between controls, mild and severe preeclamptics (p= 0.3, p= 0.4, and p= 0.8 respectively).

The values (mean ± standard deviation) of biochemical parameters (1) Serum uric acid in mg/dl → 4.9 ± 1.15 , 5.81 ± 1.08 , 7.28 ± 1.59 respectively (table -1); (2) Human TNF – α in pg/ml → 6.78 ± 1.13, 31.57 ± 9.77, 64.69 ± 11.90 respectively (table -1); and (3) Mean arterial pressure in mmHg → 83.92 ± 12.17 , 115.16 ± 17.64 , and 133.12 ± 24.61 respectively (table - 1). Highly significant results were obtained on comparing mean arterial pressure values between different groups (healthy v/s mild, healthy v/s severe and mild v/s severe) ($p < 0.001$).

Table-1: Anthropometric and Biochemical Variables of Different Subject Groups

Parameters	Healthy Pregnant Women	Mild Pre-eclampsia	Severe Pre-eclampsia
Gestational Age (Years)	33.60 ± 3.96 (28-40)	34.2 8± 3.56 (29-40)	33.76 ± 3.64 (28-40)
BMI (Kg/m^2)	29.68 ± 5.41 (18-37)	30.08 ± 6.65 (20-43)	29.88 ± 6.08 (20-42)
TNF-α (pg/ml)	6.78 ± 1.13 (4.8-8.7)	31.57 ± 9.77 (14-48)	64.69 ± 11.90 (42.20-86)
S. Uric acid (mg/dl)	4.90 ± 1.15 (2.9-7.5)	5.81 ± 1.08 (4.40-7.80)	7.28 ± 1.59 (4.20-9.90)
MAP (mmHg)	83.92 ± 12.17 (59-103)	115.16 ± 17.64 (85-139)	133.12 ± 24.61 (85-172)

MAP: Mean Arterial Pressure

Table-2: t and p Values between Different Subject Groups

Parameters	Healthy pregnant v/s Mild Pre-eclamptics		Healthy pregnant v/s Severe Pre-eclamptics		Mild Pre-eclamptics v/s Severe Pre-eclamptics	
	t	p	t	p	t	p
Gestational Age (Years)	0.62	0.4	0.35	0.7	0.91	0.3
BMI (Kg/m^2)	0.97	0.3	0.69	0.4	0.21	0.8
TNF-α (pg/ml)	25.22	0.000	48.43	0.000	21.36	0.000
S. Uric acid (mg/dl)	6.13	0.000	11.50	0.000	7.77	0.000
MAP (mmHg)	15.07	0.000	17.37	0.000	5.99	0.000

MAP: Mean Arterial Pressure

Table-3: Pearson's Correlation Analysis between S. TNF-α and S. Uric Acid in Different Subject Groups

Subjects Groups	r	p
Healthy pregnant	0.07	0.44
Mild Pre-eclamptics	0.20	0.002
Severe Pre-eclamptics	0.11	0.02

The significantly higher values ($p < 0.001$) of TNF – α observed in severe patients compared to mild and healthy controls in the present study, signify the role of TNF–α interpreting complication of pregnancy. Table 2 depicts significantly higher mean values of serum uric acid in mild and severe pre-eclamptics compared to healthy pregnant subjects and between, mild and severe patients ($p < 0.001$)

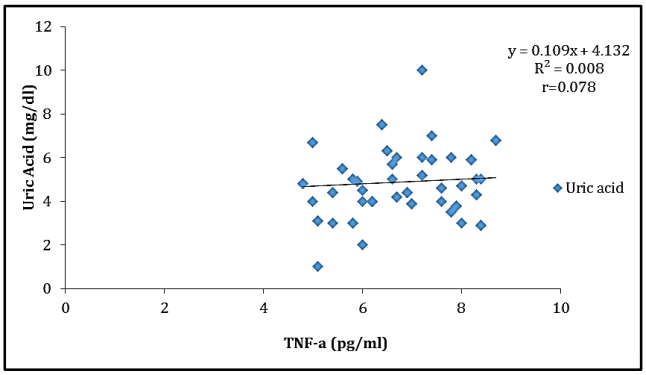

Figure-1: Correlation between S. TNF-α (pg/ml) Values & S. Uric Acid (mg/dl) Values in Healthy Controls (The black trend line depicts linear significant correlation $P < 0.001$)

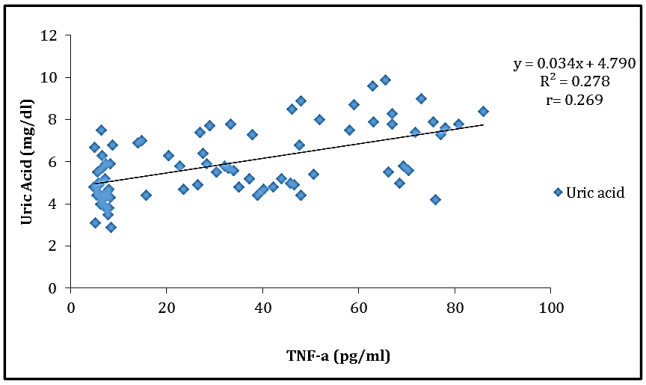

Figure-2: Correlation between S. TNF-α (pg/ml) Values & S. Uric Acid (mg/dl) Values in Mild Pre-eclamptics (The black trend line depicts linear significant correlation $P < 0.001$)

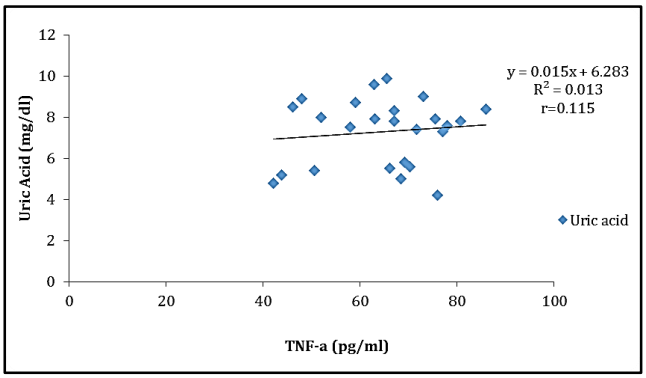

Figure-3: Correlation between S. TNF-α (pg/ml) Values & S. Uric Acid (mg/dl) Values in Severe Pre-eclamptics (The black trend line depicts linear significant correlation $P < 0.001$)

The role of TNF-α in causing complications of pregnancy can be further elucidated by its positive correlation with uric acid in various related groups of subjects. In the present study, uric acid values correlated highly significant with TNF-α values in mild patients [r=0.2, p =0.002] and in severe group the correlation is positive significant [r=0.1, p =0.02], while in healthy

pregnant women a positive association [r=0.07, p =0.44] was found. The data of this study showed raised uric acid level was also significantly and positively associated with TNF-α levels if both case and control were considered together. The indication may be that TNF-α as well as uric acid levels in blood are strongly associated and may have a role in the pathophysiology of the disease.

Discussion

In the present study, Mean arterial blood pressure level was significantly elevated in severe pre-eclamptics compared to mild pre-eclamptics (p<0.0001). These results emphasize that pre-eclampsia is characterized by hypertension. Pre-eclampsia appears likely that there are substances from the placenta that can cause endothelial dysfunction in the maternal blood vessels of susceptible women. While blood pressure elevation is the most visible sign of the disease, it involves generalized damage to the maternal endothelium, kidneys, and liver, with the release of vasoconstrictive factors being secondary to the original damage. Therefore, monitoring of hypertension in pre-eclampsia will result in a significant improvement of many pathways supposed to be involved in pre-eclampsia complications.

Serum TNF-α levels were significantly high in pre-eclamptic subjects both mild and severe patients as compared to controls (p<0.0001). Further, TNF-α levels were higher in mild pre-eclamptics as compared to severe pre-eclamptic women (p<0.0001). The expression of pro-inflammatory cytokines is up-regulated by metabolic inflammation. This leads to a generalized systemic maternal inflammatory cascade. These new findings are consistent with the concept that the maternal syndrome of pre-eclampsia is associated with endothelial dysfunction and provide evidence that at least part of this dysfunction could arise from excessive release of TNF-α into the circulation.

High uric acid values were obtained in mild & severe pre-eclamptic women (p<0.0001) as compared to healthy pregnant controls. An elevated level of uric acid reflects the degree of placental cell destruction, reduced renal clearance as well as severity of disease.[13] A significant association was seen between TNF-α and uric acid levels in mild and severe pre-eclamptic women (p<0.001; p<0.06). These also showed statistically significant linear relationship. This suggests that there is collaboration between these two parameters.

In the present review, markers of maternal predisposition, placental implantation, vasomotor regulation and endothelial dysfunction are investigated as candidate markers in the early prediction of pre-eclampsia.

Conclusion

Our findings indicate that higher levels of the inflammatory biomarker i.e. TNF-α in mild and severe pre eclampsia than normal pregnancy and also, these results suggest that these markers are increased more in severe pre-eclampsia than mild pre-eclampsia. Hence, it is felt that they may be useful in prediction and diagnosis of the severity of pre-eclampsia.

Thus, these pre-eclampsia biomarkers are in development and being evaluated on auto-mated immunoassay platforms. If these markers prove to have adequate sensitivity and positive-predictive value in screening for preeclampsia, labs will have the opportunity to help improve the quality of care for outcomes of obstetrical patients. With these new biomarkers, earlier prediction of pre-eclampsia in high-risk pregnancies will allow obstetricians to treat women earlier and hopefully improve outcomes for both the mother and the fetus.

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Cite this article as: Mittal P, Bansal A, Goyal S, Jain K, Goyal A. Association of TNF – α and uric acid in women with pre-eclampsia. Int J Med Sci Public Health 2013; 2:1032-1036.
Source of Support: None
Conflict of interest: None declared