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Original Research Article

Role of Serum Nitric Oxide and Serum Uric Acid in Essential Hypertension

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Abstract:

Background: Essential Hypertension (EHT) affects 25% of the world's population and is a major cause of stroke, congestive heart failure, end stage renal disease and myocardial infarction. The routine evaluation of essential hypertensive patient should include complete hemogram, microscopic urinalysis, albumin excretion, serum creatinine, blood urea, serum sodium, potassium, Fasting blood glucose levels and lipid profile. Uric Acid play pathogenic role in hypertension (HTN) mediated by several mechanisms and L-arginine nitric oxide pathway has an important role in hypertension, renal disease, inflammation and atherosclerosis.

Objectives: The aim of this study was to determine level of nitric oxide, uric acid, urea and creatinine in Essential Hypertensive patients as compare to controls.

Methodology: This is a case control study, in which 30 patients with Essential Hypertension and 30 normal individuals as controls were analyzed for serum nitric oxide, urea, creatinine and uric acid.

Results: In present study blood urea, serum creatinine and serum uric acid levels were significantly higher while Serum nitric oxide levels were significantly low in EHT patients when compared with that of controls.

Conclusion: We conclude that uric acid and nitric oxide along with routine kidney function tests like serum creatinine and blood urea will help in the management and treatment of essential hypertensive patients.

Keywords: Essential Hypertension, Nitrous Oxide, Uric Acid, Urea, Creatinine.

Background

Essential Hypertension is the most common type of hypertension (HTN) where there is no underlying cause for HTN. About 90-95% of cases are described as Primary (Essential) hypertension.[1] Essential Hypertension affects 25% of the world's population and is a major cause of stroke, congestive heart failure, end stage renal disease and myocardial infarction.[2,3,4]

Hypertension is usually readily detectable, easily treatable condition but if left untreated may lead to serious complications. In considerable proportion of cases, the disease tends to be asymptomatic for prolonged time, hence also labelled as 'Silent Killer'.[5] The factors linked to essential hypertension are age, obesity, smoking and stress.[6] Essential Hypertension is commonly associated with metabolic disturbances and multisystem structural damage that conspire to enhance cardiovascular risk that can be attributed to blood pressure (BP) alone.[7]

L-arginine nitric oxide pathway may play an important role in hypertension, renal disease, inflammation and atherosclerosis. It has been suggested that effect of blood flow, shear stress and other related mechanical stimuli accounts for the increased production of nitric oxide and expression of endothelial nitric oxide synthase (eNOS).[8] Restoration of NO activity can induce regression of pre-existing intimal lesions [8]. Its stable oxidative end product nitrite and nitrate diffuse into the circulation and is finally excreted in urine. Reduced level of nitric oxide (NO) synthesis and release may be resulted from decreased NOS expression, or accelerated break down of NO by the enhanced formation of reactive oxygen species, mostly the superoxide anion.[11]

Uric acid is also thought to play pathogenic role in hypertension mediated by several mechanisms such as inflammation, vascular smooth muscle cell proliferation, in renal microcirculation, endothelial dysfunction and action of rennin-angiotensin-aldosterone system.[9] Vakil A et al.[12] study on relation between severity of hypertension to serum uric acid level found that there is definite relation between serum uric acid levels and hypertension in patients and the serum uric acid levels were found to be directly proportional to the duration and severity

of hypertension. Hence the possibility of serum uric acid acting by the production of free radicals and causing oxidative stress leading to hypertension and whether the duration and severity of hypertension lead to renal dysfunction in the form of nephrosclerosis leading to higher levels of serum uric acid has to be considered as various other studies have also shown.

To decrease end organ damage and cardiovascular disease in the in the hypertension patients, there is increasing focus on the identification of the novel risk markers that would be helpful to stratify overall risk.[10] There is a need for good quality studies focusing on essential hypertension and its treatment in Indians to develop optimal strategies for essential hypertension management. Special guidelines for desirable level of risk factors may be necessary for prevention of essential hypertension. However, a very few studies have been done to investigate the correlation between the nitric oxide (NO) and essential hypertension. Considering the above facts, the present research was carried to assess the status of serum nitric oxide(NO) levels and serum uric acid levels in essential hypertension and whether any coexisting correlation with severity of the disease.

Aim and Objectives

Aim: To determine level of nitric oxide, uric acid, urea and creatinine in serum of essential hypertension patients and to find out association of these biochemical parameters with Essential Hypertension.

Objectives: To estimate levels of nitric oxide, uric acid, urea and creatinine in Essential Hypertensive patients and controls.

Methodology

This case control study was conducted at Department of Biochemistry in a tertiary care teaching hospital. Institutional Ethical Committee permission was obtained prior to commencement of the study. Hypertension patients, who were newly diagnosed by clinicians during the study period were Included in the study and their blood samples were collected. Study includes total 60 subjects attending Medicine OPD of Tertiary Care Hospital out of which 30 were Essential Hypertensive patients, while 30 were normal age and sex matched healthy controls. Patients in the age group of 35-60 years attending Medicine OPD of Tertiary Care Hospital and diagnosed as having essential hypertension Systolic Blood Pressure (SBP) ≥160 mmHg and Diastolic Blood Pressure (DBP) ≥100 mmHg and patients giving informed consent to participate in the study were included. Family history of patients noted.[13] Control group consists of subjects attending OPD, but without hypertension and with age and sex matched with patients and giving informed consent to participate in the study were included. The subjects having other diseases like tuberculosis, diabetes mellitus, malignancy, stroke, any other cardiac diseases, hepatic and renal disease, gout, pregnancy and autoimmune diseases and patients declining informed consent were excluded from the study. Data was statistically evaluated by employing standard Chi-square test.

The informed consent was obtained from participants. Blood samples were withdrawn by using 20-gauge stainless steel disposable needles, from anticubital vein with aseptic precautions. Serum samples were preserved at a 0-4^{0}C until tested. The biochemical parameters assessed in this study are serum nitric oxide by nitric oxide assay. Since NO is oxidized to nitrite and nitrate, it is common practice to quantitate total NO2 - /NO3 - as a measure for NO level. This Nitric Oxide Assay Kit is designed to accurately measure NO production following reduction of nitrate to nitrite using an improved Griess method.[24], urea by urease/GLDH method, creatinine by Jaffe's method, uric acid by uricase/ PAP method by using standard kit methods.

Results

This study included 30 essential hypertensive patients as cases, out of the 24 healthy controls, 21 (70%) were males and 9 (30%) were females. In the patient's group, a total number of the males were 24 (80%) and 6 were females (20%). The mean age for healthy controls group was 46.00±7.50 with range of 35-60 years and for hypertensive patients was 50.60±6.97 with range of 35-60 years. Table 1 and 2 showed the study of age and sex distribution among the study groups.

Table 1: Distribution of Patients and Controls

Groups	Age(Years) (Mean±SD)	Number
Patients	50.60±6.97	30
Controls	46.00±7.50	30

Table 2: Gender wise distribution of study groups

Gender	Patients		Controls	
	Number	%	Number	%
Male	24	80	21	70
Female	06	20	09	30
Total	30	100	50	100

Table 3: Family history of hypertension in Patients and Controls

Family History	Patients (n=30)	Controls (n=30)	Total	p value
Positive	23 (77%)	9 (30%)	32	<0.05*
Negative	7 (23%)	21 (70%)	28	

*p<0.05 is considered to be significant

Above table showed the study of family history among the study groups. Applying Chi-square test, it was found that family history of hypertension is positively correlated (0.032) to the development of essential hypertension which is statistically significant (p<0.05).

Table 4: Study of BMI, Systolic BP and Diastolic BP among the patients and controls

Parameters	Mean±SEM		p value
	Patients (n=30)	Controls (n=30)	
BMI (Kg/m2)	26.5 ± 1.43	24.57 ± 0.05	NS
SBP (mm Hg)	158.0 ± 3.1	121.0 ± 1.67	<0.05
DBP (mm Hg)	94.3 ± 1.53	76.3 ± 1.34	<0.05

Above table shows the comparison of body mass index (BMI), systolic, and DBP among the healthy controls and hypertensive patients. Comparison of BMI between the hypertensive patients and healthy controls show no statistically significant (p>0.05) difference. We found a highly significant rise (p<0.05) in both systolic and diastolic BP in hypertensive patients as compared to controls.

Table 5: Biochemical Parameters in Patients and Control

Parameters	Patients (n=30) Mean±SD	Control (n=30) Mean±SD	p value
Nitric Oxide (µmol/l)	9.73±3.01*	21.79 ±4.75	*(P<0.001)
Uric Acid (mg/dl)	6.49±0.83 *	4.22±0.61	*(P<0.001)
Urea (mg/dl)	33.17±6.98*	21.17±2.08	*(P<0.001)
Serum Creatinine (mg/dl)	0.94±0.13*	0.65±0.18	*(P<0.001)

*(P<0.001) Highly Significant

The statistical method used to compare data is (t) test: Above table shows the comparison of serum nitric oxide, uric acid, urea, creatinine levels among the healthy and hypertensive patients. It was found that significantly increased levels of serum uric acid, urea, creatinine (p<0.001). We found a highly significant decreased (p<0.001) serum NO (nitrite) levels in essential hypertensive patients when compared to healthy control group.

Discussion

Hypertension is the most common cause of cardiovascular disease. (14) Essential Hypertension accounts for more than 90% of cases of Hypertension (HTN).

Hypertension is the most attributable cause for 57% of stroke and 24% of coronary heart disease deaths in India. India is the second most populous country in the world and emerging burden of cardiovascular disease in counties here is alarming.

Nitric Oxide is a free radical that is considered to be the major endothelium derived relaxing factor and is released from endothelial cells in response to shear, stress or stimulation of several receptors on the endothelial cell surface. Decreased expression of NOS may be the cause of reduced level of NO synthesis and release.

Our results show negative association of NO concentration with HTN. Decreased NO level in EHT patients as compared to control may be related to endothelial dysfunction.

Few studies have shown that NO levels are diminished in essential hypertension, and therapeutic control of BP leads to restoration of NO level in these patients. In this study, most of the hypertensive patients (73%) fall in the age group of 40-55 years. The family history of hypertension was found in 64% patients but only in 30% of healthy control group which was found to be significantly correlated to the development of essential hypertension.

Similar results were obtained by M. Chandra et al (2003) [15], P. Moriel et al (2002) [16], Dr. Sasirekha et al (2016) [6].

We observed significantly increased (P<0.001) serum uric acid level in patients as compared to healthy controls. Our results show that HTN is associated with increase in uric acid concentration. In present study, increased serum uric acid level in EHT patients as compared to controls is may be due to reduced renal tubular secretion, activation of the renin-angiotensin system.[17] Potential mechanisms involved with the association of rise in uric acid concentration and HTN include decreased renal blood flow (decreased GFR) stimulating urate reabsorption, microvascular (capillary) disease resulting in local tissue ischemia, ischemia with associated increased lactate production that blocks

urate secretion in the proximal tubule and increase uric acid synthesis due to increased RNA–DNA breakdown and increased purine (adenine and guanine) metabolism, which increases uric acid and ROS through the effects of xanthine oxidase. Increased serum uric acid level may be due to tubular secretion which may reflect early renal vascular alteration with reduction in cortical blood flow and depressed tubular secretion of urate cause by its reduced delivery to the tubular secretary sites.

Similar results were obtained by, Samia Jawed et al (2005) [18], Kumral Cagli et al (2015)[10], Kashem MA et al (2011)[17], Mohammad Shah et al (2015)[19].

We also observed significantly increased (P<0.001) blood urea levels in EHT patients as compared to healthy controls. The elevation may be relevant to the decreased Glomerular filtration rate (GFR) as a result of HTN effect on renal function. A reduction in renal blood flow may lead to a decrease of GFR, this may lead to decreased distal tubular flow rate which can increase urea reabsorption and decreased secretion which may be the reason for elevated serum urea concentration.

Similar results were obtained by Isra'a H et al (2010) [20], Rihab A.M et al (2015) [2], Dr.Rakhee Yadav et al (2014).[21]

The mean level of creatinine is in normal range for both control and patients. But, significantly increased (P<0.001) serum creatinine levels were observed in patients as compared to healthy controls.

Our results show association of creatinine concentration HTN. Similar results were obtained by Isra'a et al (2010) [20], Sarkar D et al (2006) [22], Dr Rakhee Yadav et al (2014) [21], Pooja and Yashoda Mittal et al (2014) [23].

The rise in serum creatinine concentration may be attributed to the decrease in creatinine clearance due to the decrease in GFR in EHT patients.

Conclusion

In our study, serum nitric oxide was significantly decreased in EHT patients. Blood urea, serum creatinine and serum uric acid levels were significantly higher in EHT patients when compared with that of controls. The observed alterations may be due to renal and endothelial dysfunction respectively. We conclude by above mentioned findings that there's a significant correlation between nitric oxide and essential hypertension, also there was found to be a significant correlation between uric acid levels and EHT.

Based on this study, serum uric acid levels can be used as a determinant for severity of hypertension. Further researches needs to be carried out in the context of lowering serum uric acid levels for management of hypertension and its monitoring in order to alter its course. More studies may help in the understanding of nitric oxide's role in regulating the BP and its use in appropriate medical intervention in the early phase of disease. The lower level of NO in hypertensive patients suggests that the estimation of NO along with serum uric acid can be included as a routine laboratory work-up for screening people for hypertension and for risk management in newly diagnosed hypertensive patients.

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