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Original Research Article

Uric Acid in Hypertension: A Marker of Oxidative Stress

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ABSTRACT

In this present study, the relation between serum uric acid and oxidative stress is evaluated in hypertensive patients. Hypertension is one of the conditions associated with oxidative stress. Total 30 hypertensive adults and 30 normotensive adults were investigated. Serum uric acid and serum MDA levels of all cases were done. Uric acid is found to be an antioxidant and participates in defence mechanism against oxidative stress.

Key words: Uric acid, Oxidative stress, Hypertension, Hyperuricemia, MDA

INTRODUCTION

Hyperuricaemia is a common finding in hypertensive patients. It is possible that uric acid is a marker for xanthine oxidase-associated oxidants and that the latter could be driving the hypertensive response. Also uric acid concentrations seem to play key role in oxidative stress defence factors. Uric acid is an important evolutionary antioxidant substitute for the loss of the ability to synthesize ascorbate in higher primates. [1-3] In this study, we are evaluating whether uric acid can be a marker of oxidative stress in patients with hypertension. Hyperuricemia is linked to obesity,[4] hypertension, [5] reduced HDL cholesterol, [6] hypertriglyceridemia, [7] hyperinsulinemia and reduced insulin sensitivity, [8] components of the metabolic syndrome.

In normal subjects, sympathetic nervous system stimulation induced by norepinephrine or angiotensin II infusion causes a simultaneous increase in serum uric acid levels and blood pressure. These changes were reversible after the discontinuation of the pressure agent.[9] Serum uric acid levels have been reported to be inversely related to renal blood flow and directly to renal vascular resistance in both normotensive and hypertensive humans. [10,11] Hyperuricemia has been associated with elevated circulating endothelin levels [12] and one of the major sites of the production of uric acid in the cardiovascular system is the vessel wall and particularly the endothelium.

Potential mechanisms involved with the association of hyperuricemia and hypertension include the following:

1. Decreased renal blood flow (decreased GFR) stimulating urate reabsorption,

2. Microvascular (capillary) disease resulting in local tissue ischemia.
3. Ischemia with associated increased lactate production that blocks urate secretion in the proximal tubule and increased uric acid synthesis due to increased RNA-DNA breakdown and increased purine (adenine and guanine) metabolism, which increases uric acid and ROS through the effect of xanthine oxidase (XO).
4. Ischemia induces increased XO production and increased serum uric acid (SUA) and reactive oxygen species(ROS).

Because endothelial dysfunction, local oxidant generation, elevated circulating cytokines, and a proinflammatory state are common in patients with cardiovascular disease and hypertension there is an increased level of oxidative – redox stress within vascular tissues. Oxidative – redox stress results in impaired endothelium-dependent vasodilation with quenching of endothelial nitric oxide (eNO) [13] and allows the endothelium to become a net producer of ROS specifically superoxide as the endothelial nitric oxide synthase (eNOS) enzyme uncouples to produce superoxide instead of eNO. [14]

MATERIALS AND METHODS

The study was carried out in Department of Biochemistry and central Investigation Laboratory in MGM Hospital, Aurangabad.

The Protocol of the study was submitted to the institutional Ethical Committee and permission was granted for the study.

Study groups:

Cases- 30 patients aged 35-60 years with systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg of MGM Medical College, Aurangabad.

Controls- 30 normotensive healthy controls (age and sex matched) belonging to the same socio-economic status.

Blood sampling:

The blood samples (3-5ml fresh blood) will be drawn and collected in a clean, disposable plastic tube from anterior cubital vein under aseptic condition for estimation of serum uric acid and serum MDA (Malondialdehyde) levels.

Serum uric acid levels were done by Two-Dimentional RXL. Concentration of serum MDA (Malondialdehyde) levels was estimated by Nourooz Zadeh's method. [15]

Blood pressure was measured by standard techniques, using 140/90 mmHg for diagnosis of hypertension.

Statistical analysis:

The data were evaluated by SPSS statistical package version 16.0. The results obtained were statistically analyzed by using student t-test. Value of uric acid was given in mg/dl. Systolic and diastolic blood pressure was measured in mm of Hg. All Values were expressed as mean ± standard. The results were considered significant when $p < 0.05$.

RESULT

Table 1 shows the mean values of systolic and diastolic blood pressure in cases and controls. The mean of systolic and diastolic blood pressure in cases was 152.44 and 100.46 respectively, which were significantly higher as compared with the control groups.

Table 1: Mean of systolic and diastolic blood pressure in cases and Controls.

Blood pressure (mm of Hg)	Cases of Hypertension (n=30)	Normotensive Controls (n=30)	p-value
Systolic Blood Pressure	152.44 ± 6.35	126.78± 10.45	0.002
Diastolic Blood Pressure	100.46 ± 5.63	83.35± 8.34	0.001

Values are given as mean ± SD.
p-value <0.05 considered as statistically significant.

The results in this study showed significant increase in serum uric acid levels in hypertensive patients as compared to controlled normotensive group ($p<0.05$) as shown in table 2. There was a significant increase in the levels of serum MDA levels in cases as compared to controls ($p<0.05$) as shown in table 2.

Table 2: Mean of serum uric acid and serum MDA levels in cases and Controls.

Parameter	Cases of hypertension (n=30)	Normotensive Controls (n=30)	p-value
Serum uric acid (mg/dl)	6.973± 0.518	4.413±0.0.878	0.001
Serum MDA (nmol/ml)	4.69±0.7567	1.145±0.166	0.004

Values are given as mean ± SD.
p-value <0.05 considered as statistically significant.

DISCUSSION

Hypertension is a major contributor pathologies associated with vascular functional and structural changes including endothelial dysfunction, altered contractility, and vascular remodeling. Central to these phenomena is oxidative stress. Reactive oxygen species influence vascular, renal, and cardiac function and structure by modulating cell growth, contraction/dilatation, and inflammatory responses via redox-dependent signaling pathways.

Uric acid is one of the major endogenous water-soluble antioxidants of the body. [13] High circulating uric acid levels may be an indicator that the body is trying to protect itself from the deleterious effects of free radicals by increasing the products of endogenous antioxidants, eg, uric acid. Interestingly, uric acid prevents oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilatation in the face of oxidative stress. [13]

The endothelium is an elegant symphony responsible for the synthesis and secretion of several biologically active molecules. It is responsible for regulation of vascular tone, inflammation, lipid metabolism, vessel growth (angiogenesis - arteriogenesis), arterial vessel wall - capillary sub endothelial matrix remodeling, and modulation of coagulation and fibrinolysis. One particular enzyme system seems to act as the maestro: The endothelial nitric oxide synthase (eNOS) enzyme and its omnipotent product: endothelial nitric oxide (eNO).

The endothelial nitric oxide synthase (eNOS) enzyme reaction is of utmost importance to the normal functioning of the endothelial cell and the intimal interstitium. When this enzyme system uncouples the endothelium becomes a net producer of superoxide and ROS instead of the net production of the protective antioxidant properties of eNO.

There are multiple causes for endothelial uncoupling in addition to hyperuricemia. Xanthine oxidase - oxioreductase (XO) has been shown to localize immunohistochemically within atherosclerotic plaques allowing the endothelial cell to be equipped with the proper machinery to undergo active purine metabolism at the plasma membrane surface, as well as, within the cytoplasm and is therefore capable of overproducing uric acid while at the same time generating excessive and detrimental ROS . The healthy endothelium is a net producer of endothelial nitric oxide (eNO). [14]

The activated, dysfunctional endothelium is a net producer of superoxide (O_2^-) associated with MS, T2DM, atherosclerotic and hypertension. [14]

CONCLUSION

It is concluded from the results of this study that hypertension is responsible for the mechanisms of the generation of reactive oxygen species and the vascular effects of oxidative stress. Hyperuricemia

prevents oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilatation in the face of oxidative stress. Hence Serum uric acid thus generated can act as a marker of oxidative stress in patients with hypertension.

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