Uric Acid and Endothelial Dysfunction in Essential Hypertension

Zainab Abdul Razak AL-SharifiA, Halla Ghazi Mahmood

ABSTRACT:

BACKGROUND:

Uric acid can stimulate the synthesis of c-reactive protein, and that might be one of the mechanisms underlying the endothelial dysfunction. Several studies showed an independent link between UA and CRP suggest that chronic exposure to mild hyperuricemia may be a factor that contributes to micro inflammation and raised CRP in individual the essential hypertension.

OBJECTIVE:

To investigate the relationship between the serum uric acid, C-RP , total cholesterol and endothelial dysfunction in patient with essential hypertension.

PATIENTS AND METHODS:

Twenty patients with essential hypertension and fifteen apparently healthy subjects matched for age and weight have been included in this study,uric acid and total cholestrol were determined by enzymatic methods, high sensitivity C-reactive protein (HsCRP) enzyme immunoassyfor the quantitative determination in human serum was used.

RESULTS:

The data obtained showed that the serum levels of uric acid, C-Reactive protein and total cholesterol were significantly higher in patients with Hypertension than in healthy controls.

CONCLUSION:

The conclusion was that hyperuricemia in individuals with essential hypertension is associated with endothelial dysfunction.the hypothesis that uric acid plays a significant role in this alteration in humans.

KEY WORDS: uric acid, C-Reactive protein,hypertension.

INTRODUCTION:

The association of hyperuricemia with hypertension has long been recognized[١]. It remains unresolved whether the association of hyperuricemia with hypertension is solely because of underlying renal and metabolic abnormalities . Extensive epidemiologic and experimental evidence now suggests that serum uric acid(UA) is a relevant and independent risk factor for cardiovascular and renal disease, particularly in patients with hypertension, heart failure, or diabetes .Hyperuricemia predicts mortality in patients with heart failure or coronary heart disease[٢], cerebrovasclar events in individuals with diabetic and cardiac ischemia in hypertension . The mechanism(s) by which UA may engender organ damage is still incompletely understood, but there is increasing evidence that endothelial dysfunction is a fundamental mechanism whereby this substance may affect cardiovascular and renal function and structure[٣]. The relationship between UA levels and endothelial dysfunction has been explored only in a study that combined seemingly healthy individuals and patients with preexisting cardiovascular disease of various severity or in individuals at increased cardiovascular risk[٤]. Essential hypertension is consistently associated with endothelial dysfunction ,and hyperuricemia is a strong predictor of hypertension and BP progression[٥]. Therefore, individuals with essential hypertension constitute an interesting population in which to investigate the relationship between UA and endothelial dysfunction. It is noteworthy to mention that focusing on a drug –free population without cardiovascular complications seems important because these factors are notorious confounders in the interpretation of hemodynamic tests of endothelial function[٦].

Uric acid can stimulate the synthesis of c-reactive protein, and that might be one of the mechanisms underlying the endothelial dysfunction.

Deparment of Biochemistry\College of Medicine\University of Baghdad.

Several studies showed an independent link between UA and CRP suggest that chronic exposure to mild hyperuricemia may be a factor that contributes to micro inflammation and raised CRP in individual the ssential hypertension[٧].

The aim of this study is to investigate the relationship between the serum uric acid, C-RP , total cholesterol and endothelial dysfunction in patient with essential hypertension .

MATERIAL AND METHODS:

This study had included twenty patients with essential hypertension (١٢ male and ٨ female) with age ranged between ٤٠-٦٠ years and fifteen apparently subjects matched for age and weight have been studied, attending the out patients consultation clinic of Baghdad teaching hospital in medical city, in a period from October ٢٠١٢– march ٢٠١٣.

- All patients underwent a clinical examination to exclude the presence of secondary hypertension.

-Essential hypertension was defined as a diastolic blood pressure ≥ ٩٠ mmHg, systolic blood pressure ≥ ١٤٠ mmHg, or self-reported use of antihypertensive medication.

Blood was taken from antecubital vein with the patient in the recumbent position after an overnight fast.

-Total cholesterol was determined by enzymatic methods as its one of the metabolic risk factors on hypertension[٨].

-Uric acid was determined using enzymatic methods based on the measurement of Jaffe chromogen and by the URICASE/ POD method implemented in an autoanalyzer,

high sensitivity C-reactive protein (HsCRP) enzyme immunoassay for the quantitative determination in human serum was used.DRG international Inc. USA . Which is done by ELISA test [٩].

Statistical Analyses:

Descriptive statistics for all data of each set were expressed as mean ± SD and the percent of abnormal value in any test was calculated as above or below the mean ± SD of the normal value for the matched control group, were compared using independent sample (t)test p<o.oo٥ were considered statistically significant.

The overall predictive values for the results in the studied groups were performed according to program of office xp.

RESULTS:

Results obtained in the present study showed that the serum levels of uric acid, C-Reactive protein and total cholesterol were significantly higher in patients with Hypertension than in healthy controls. are shown in table(١).

Table١:Mean ±SD of serum uric acid, and C-Reactive protein in patients and healthy controls.

Type	Patients (n=٢٠) Mean ±SD	control (n=١٥) Mean ±SD
Uric acid(mg/dl)	٨,٠٣± ٣,٥٠	٤,٣٢±١,٠٧
C-Reactive protein(mg/ml)	٥,٦ ±١,٦٩	٣,٨ ±١,١٥
Total Cholestrol(mg/ml)	١٦٤±٥٣,٤	١٣٨±٩,٤

DISCUSSION:

This study shows that serum UA concentration in individuals with uncomplicated, untreated essential hypertension is associated with endothelial dysfunction independent of traditional and emerging risk factors.

Endothelial dysfunction, commonly observed in cardiovascular and renal diseases, is attributed to oxidative stress, dyslipidemia (elevated total cholesterol level in the blood), accumulation of endogenous inhibitors of nitrous oxide synthase, genetic factors, and other causes[٩]. Few studies were conducted in human and available data are controversial .In patients with heart failure [١٠], with type ٢ diabetes[١١], at increased cardiovascular risk[١٢], and with hypercholesterolemia but not in patients with essential hypertension[١٢], allopurinol, a xanthine oxidase inhibitor that lowers UA and interacts with anion superoxide generation [١٣], improves endothelial dysfunction. In the study of Mercuro et al[١٤], the beneficial effect of allopurinol could have been a direct consequence of the reduced UA levels rather than of superoxide anions mediated by xanthin oxidase inhibition because of the close correlation found between the amount of

that decrease and the improvement of endothelial function.

High UA levels have been associated with organ damage in hypertensive patients and are considered an integral part of the biochemical alterations that compound the metabolic syndrome. Indeed, serum UA is higher in hypertensive patients with target organ damage[١٥] ,as well as in seemingly healthy men[١٦].

These data suggest that chronic exposure to mild hyperuricemia is a factor that contributes to endothelial dysfunction in patients with uncomplicated, untreated primary hypertension. Inflammation may be a relevant pathway in cardiovascular damage caused by uric acid[١٧]. The hypothesis that UA may act as a proinflammatory agent is supported by observations of patients with heart failure [١٨] .and recently in an elegant experimental study [١٧]. These data demonstrate that UA can stimulate the synthesis of CRP, and that might be one of the mechanisms underlying the endothelial dysfunction. these data are showing an independent link between UA and CRP suggest that chronic exposure to mild hyperuricemia may be a factor that contributes to micro inflammation and raised CRP in individuals with essential hypertension. In this regard , it is important to note that in this and in a previous study [١٩]. The observation that the UA –endothelial function link remains strong also in a statistical model that included CRP suggests that inflammation – independent pathways play a significant role in the putative effect of UA on endothelial function . Serum uric acid showed an association with subsequent cardiovascular event and death from all causes. Such association was clinically consistent and independent of many potential confounders including age,gender,body mass index,diabetes, TC\HDL-C [٢٠]. At entry into the study , when serum uric acid was determined , all subjects were untreated important concomitant disease were excluded.

This study has several limitations . The cross-sectional design does not allow establishment of the direction of causality; therefore, our observation remain to be confirmed in prospective observational and interventional studies . Second , ours is a tertiary referral center ; therefore , patients who enrolled in this survey represent a selected population that is not representative of primary care .Third , we cannot exclude that UA constitutes a measure of residual confounding from Framingham risk factors, e.g. That relatively higher UA concentration may be expression of a longer exposure to hypertension and \or to dyslipidemia.

From this study we conclude that hyperuricemia in individuals with essential hypertension is associated with endothelial dysfunction. This association, which is independent of classical risk factors supports the hypothesis that uric acid plays a significant role in this alteration in humans. Interventional studies are needed to clarify the nature of this association.

REFERENCES:

١-Anker SD, Doehner W, Rauchhaus M, Sharma R, Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging.Circulation ٢٠٠٣;١٠٧:١٩٩١-٩٧.

٢- Mehmet Kanbay, Mark Segal, Baris Afsar, Duk-Hee Kang .The role of uric acid in the pathogensis of human cardiovascular disease. [Heart Online] ٢٠١٣; ٢٣.

٣- D'Elia, L; Ippolito, R; De Palma, D; Russo, Serum Uric Acid Predicts the Development of Hypertension in A Sample of Male Normotensive Adults: ١B.٠.J of Hypertention ٢٠١٢;٦.

٤- Sánchez-Lozada LG, Tapia E, Santamaría J,Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats.Kidney Int ٢٠٠٥;٦٧:٢٣٧-٤٧.

٥-Anna-Karain E,Bonamy. Uric Acid and the Developmental Origins of Hypertension. Am J Hypertens ٢٠٠٩;٢٢:٣٤٩.

٦- Mercuro G, Vitale C, Cerquetani E, Zoncu S. Effect of hyperuricemia upon endothelial function in patients at increased cardiovascular risk.Am J Cardiol ٢٠٠٤;٩٤:٩٣٢-٣٥.

٧-Feiq DI. The role of uric acid in the pathogenesis of hypertension in the young. J Clin Hypertens. ٢٠١١;١٤:٣٤٦-٥٢.

٨-Johson RJ,Feig DI,Herrera-Acosta RB. resurrection of t cholesterol as a causal risk factor in essential hypertension.Hypertention ٢٠٠٥;٤٥:١٨-٢٠.

٩-Hanspeter Brunner, John R Cockcroft, John Deanfield, Ann Donald, Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertens.J Hypertention ٢٠٠٥;٢٣:٢٣٣-٤٦.

١٠- **Perticone F, Maio R, Tripepi G, Zoccali C.** Endothelial dysfunction and mild renal insufficiency in essential hypertension.Circulation ٢٠٠٤;١١٠:٨٢١-٢٥.

١١- Francesco Perticone, MD; Roberto Ceravolo, MD; Arturo Pujia, MD; Giorgio Ventura, MD; Prognostic Significance of Endothelial Dysfunction in Hypertensive Patients.Circulation٢٠٠١;١٠٤:١٩١-٩٦.

١٢-Wan-Jing Ho[١], Wen-Pin Tsai[٢], Kuang-Hui Yu ,Pei-Kwei. Association between endothelial dysfunction and hyperuricaemia.Rheumatology ٢٠١٢;٤٩:١٩٢٩-٣٤.

١٣-Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol ٢٠٠٥;١٦:٣٥٥٣-٦٢ .

١٤-Li JM, Shah AM. Endothelial cell superoxide generation: regulation and relevance for cardiovascular pathophysiology. Am J Physiol Regul Integr Comp Physiol. ٢٠١٠;٢٨٧:١٠١٤-٣٠.

١٥-Tuttle KR, Short RA, Johnson RJ. hypothesis fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome.NatClinPractNephrol.٢٠٠٥; ١:٨٠-٨٦.

١٦-Waring WS, Adwani SH, Breukels O, Webb DJHyperuricaemia does not impair cardiovascular function in healthy adults.Heart ٢٠٠٤;٩٠:١٥٥-٥٩.

١٧-Mazzali M, Kanbay M, Segal MS, Shafiu M. Uric acid and hypertension: cause or effect. Curr Rheumatol Rep. ٢٠١٠;١٢:١٠٨-١٧.

١٨-Corina erban, gan, Ruxandra Christodorescu.Association of Serum Uric levels and Carotid IntimaThickness with the Numbers of Organ Damaged inHypertensive Patients. International Journal of Collaborative Research on Internal Medicin ٢٠١١;٣.

١٩-Zocculi C,Main R,Tripepi,Mallamaci F.Inflammation as amediator of the link between mild to moderate renal insufficiency and endothelial dysfunction in essential hypertension.J Am Soc Nephrol ٢٠٠٦;١٧:s٦٤-s٦٨.

٢٠- Christine Gersch,[١] Sergiu P. Palii,[١] Kyung Mee Kim,[١] Alexander Angerhofer. Inactivation of Nitric Oxide by Uric Acid. Nucleosides Nucleotides Nucleic Acids٢٠٠٨;٢٧:٩٦٧–٧٨.