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Urinary Albumin Creatinine Ratio (ACR) and left ventricular hypertrophy in essential hypertension and its correlation with serum uric acid level: A tertiary care centre study

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Abstract:

Introduction: Hypertension is a major risk factor for cardiovascular mortality, through its effects on target organs, such as the heart and kidneys. Hyperuricemia increases cardiovascular risk in patients with hypertension. Microalbuminuria, which is best predicted by urinary albumin creatinine ratio (ACR), in hypertension is described as an early sign of kidney damage. Microalbuminuria and left ventricular hypertrophy are predictor for end stage renal disease and cardiovascular disease.

Aims and objectives: To study the association of urinary albumin creatinine ratio (ACR) and left ventricular hypertrophy with serum uric acid in untreated patients of essential hypertension, as a marker of end organ damage.

Material and methods: This is a case control study, carried out in 100 (50 females, 50 males) untreated patients of essential hypertension. 100 healthy age and sex matched non -hypertensive individuals served as controls. Uric Acid was analyzed by the enzymatic colorimetric method. Urinary albumin creatinine ratio was measured by assaying urinary albumin and creatinine in an early morning spot urine sample and left ventricular hypertrophy was evaluated by 2 D echocardiography.

Results: Mean serum uric acid was significantly higher among the patients with hypertension (7.03±1.49 mg/dl) than in the controls (4.62±1.22 mg/dl, P=0.001). Among hypertensive patients, ACR value between 30-300mg/g (microalbuminurea) was present in 53.57% of those with hyperuricemia and in 22.72% of those with normal uric acid levels (P<0.001). Left ventricular hypertrophy was more common in the hypertensive patients with hyperuricemia (67.85% versus 27.27.0% respectively; *P*=0.001).There was a significant linear relationship between mean uric acid levels and the number of target organ damage.

Conclusion: High serum uric acid is associated with target organ damage in patients with hypertension, even at the time of diagnosis; thus, it is a reliable, cost effective and early marker of diagnosing end organ damage in patients with hypertension.

Keywords: Essential hypertension, serum uric acid, microalbuminuria, hyperuricemia

INTRODUCTION:

Hypertension is one of the leading cause of global burden of diseases. Approximately 7.6 million deaths (13-15% of total) and 92 million disability life years worldwide were attributable to high blood pressure in 2001. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease, congestive heart failure, ischemic and hemorrhagic stroke, renal failure and peripheral arterial disease. Patients with blood pressure greater than 140 mm Hg systolic and 90 mm Hg diastolic with no definable cause are said to have a primary, essential or idiopathic hypertension. 95% of all hypertensive fall into this group [(1,2,3,4)].

Uric acid (UA) levels tend to be elevated in patients with hypertension[(5)]. Elevated UA is a risk factor for the development of cardiovascular disease, and the European Society of Hypertension–European Society of Cardiology guidelines recommend performing routine laboratory testing for serum UA (SUA) in patients with hypertension [(5,6)]. While it has been shown that SUA is associated with multiple cardiovascular risk factors, including hypertension, metabolic syndrome, diabetes, and renal disease, it is yet to be confirmed whether UA independently predicts adverse cardiovascular events in patients with hypertension. Various large trials have failed to identify UA as a significant and independent risk factor [(4,7)].

Microalbuminuria (MAU) is best predicted by urinary **albumin-to-creatinine ratio (ACR)**. This is done to provide a more accurate indication of the how much albumin is being released into the urine. Creatinine, a byproduct of muscle metabolism, is normally released into the urine at a constant rate and its level in the urine is an indication of the urine concentration. This property of creatinine allows its measurement to be used to correct for urine concentration when measuring albumin in a spot urine sample. Microalbuminuria is the independent risk factor to develop cardiovascular and cerebrovascular diseases. Furthermore, MAU has been described as an early sign of kidney damage and an indicator for end stage renal disease (ESRD) and cardiovascular disease [(8)]. The risk of developing renal failure, ischemic and hemorrhagic stroke and peripheral arterial disease is doubled in the presence of microalbuminuria. In a large population based study of non diabetic hypertensives, the presence of microalbuminuria is associated with significantly higher prevalence of LVH, CAD, MI, hyperlipidemia and peripheral vascular disease [(9)].

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Moderately increased albuminuria, historically known as microalbuminuria, (ACR 30-300 mg/g) refers to albumin excretion above the normal range but below the level of detection by tests for total protein. Severely increased albuminuria, historically known as macroalbuminuria, (ACR >300) refers to a higher elevation of albumin associated with progressive decline in glomerular filtration rate.

The relationship between uric acid and microalbuminuria has been observed previously in hypertensives. However, the pathophysiological mechanism underlying this association remains elusive. Infact obesity, lipid abnormalities and insulin resistance are related to hyperuricemia as well to microalbuminuria.The aim of the present study is to evaluate the association of uric acid levels with microalbuminuria and left ventricular hypertrophy in patients with essential hypertension.

Material and methods :

Study design: Hospital Based case control study conducted in New Medical College Hospital, Kota, Rajasthan.

Study Population: Total 200 patients in which 100 were normotensive controls and 100 were untreated hypertensive cases. Informed written consent was obtained from all patients and Ethical clearance had been obtained from institutional ethical Committee.

Inclusion Criteria

For Control

- 100 non hypertensive healthy, age and sex matched individuals were randomly selected from the hospital staff and patient's relatives.

For Cases

- 100 untreated hypertensive (according to JNC VII classification for hypertension) adult male and female patients > 18 years of age were included as cases.

Exclusion Criteria

Patients were excluded if they had any of the following –

- Diabetes mellitus
- Ischemic heart disease,
- All cases of secondary hypertension,
- Clinical findings of gout or extra- articular manifestations of hyperuricemia
- Obesity (BMI ≥30)
- H/o alcohol abuse
- H/o drugs known to cause hyperuricemia, e.g. thiazide diuretics
- H/o Renal disease
- H/o pre-eclampsic toxemia

Blood pressure measurement:

BP was measured with a standard mercury sphygmomanometer (with an appropriate cuff size) on the patients' right arm, as the patients were in the seated position with their feet on the floor after a 5-minute rest. The average of two BP measurements taken 5 minutes apart was used.

Based on the seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC 7 report) BP is classified into the following stages-

Table 1: Grading of hypertension (JNC 7)

Classification of BP	Systolic BP mm hg	Diastolic BP mm hg
Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	≥160	≥100

Uric acid: UA was analyzed with the enzymatic colorimetric method using an autoanalyzer. Normal values in the hospital laboratory are (3.4-7 mg/dl) and, (2.4-6 mg/dl) for men and women, respectively; therefore, individuals who had values above these levels were classified as having hyperuricemia.

Urinary Albumin Creatinine Ratio: Urinary microalbumin was measured by the immunoturbidimetric (Randox Laboratories Antrim UK) method and urinary creatinine by modified kinetic Jaffe reaction in early morning spot urine. The guidelines

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recommended using a first-morning sample because of the potentially higher correlation with 24-h albumin excretion. ACR is calculated by dividing albumin concentration in milligrams by creatinine concentration in grams.

Echocardiography: Echocardiographic studies for all the patients were carried out with an Aloka Prosound SSD 4000 echocardiography machine (Fair Medical Company Ltd, Matsudo, Japan) equipped with a 2.5 Hz transducer.With the patient in the left lateral decubitus position, targeted echocardiographic estimations were taken. These included the standard two-dimensional oriented motion–mode measurements of interventricular septal thickness in diastole, LV posterior wall thickness in diastole, and LV end diastolic diameter just beyond the tips of the mitral valve leaflets. LV mass (in grams) was automatically calculated with the internal software of the machine.

LV mass was indexed to the body surface area using cut-off values of 134 g/m^2 and 110 g/m^2 for men and women, respectively. Patients with increased LV mass index (LVMI) and increased RWT (relative wall thickness) were considered to have concentric hypertrophy, and those with increased LVMI and normal RWT were considered to have eccentric hypertrophy. Those with normal LVMI and increased or normal RWT were considered to have concentric remodeling or normal geometry, respectively.

Definition of target organ damage (TOD): TOD was defined by the presence of microalbuminuria (Spot urinary albumin creatinine ratio 30-300 mg/g or Spot urinary albumin excretion: 20–200 mg/L) or echocardiographic evidence of LV hypertrophy (LVH) defined as LVMI ≥134 g/m2 in men and ≥110 g/m2 in women.

Statistical Analysis:
All data were analyzed using the commercially available statistical package for the social sciences (SPS) version 17.0 analytic software. Data were expressed as mean ± standard deviations, and frequencies as a percentage. Continuous variables were compared with the Students t-test, or one-way analysis of variance, as considered appropriate. Relations among continuous variables were assessed using Pearson's correlation coefficient and multiple linear regression analysis. All tests were considered to be statistically significant at the P-value ≤ 0.05.

Results:
Total 200 subjects were studied, of which 100 were untreated hypertensive (based on JNC VII classification) and 100 were normotensive controls without any condition known to cause raised serum uric acid levels and microalbuminuria.
Mean age of cases was 52.82±15.02 years and of controls it was 53.54±15.03 years. There was no statistically significant difference in the mean age of the cases and controls (P=0.71). The baseline clinical and laboratory characteristics of the study population are shown in Table 2.

Table 2: Clinical and Laboratory Characteristics of study population

Variable	Case (n=100)	Control (n=100)	P value
Age	52.82± 15.02	53.54±15.03	0.71
BMI	25.11±1.58	22.74±1.50	<0.0001
SBP(MM of Hg)	166.21±14.18	115±5.28	<0.0001
DBP(MM of Hg)	93.71 ±8.08	73.64 ±6.83	<0.0001
Mean SUA	7.03±1.49	4.62 ±1.22	<0.0001
% of patients with hyperuricemia	56%	14%	<0.0001
% of patients with LVH	50%	6%	<0.0001
% of patients with MAU	40%	6%	<0.0001

Serum Uric Acid levels in male cases ranged from 4.3 mg/dl to 11.1 mg/dl and in female cases from 4.1 mg/dl to 8.8 mg/dl. Serum Uric Acid levels in male controls ranged from 3.2 – 7.9 mg/dl and female controls ranged from 3.1 – 7.9 mg/dl. Mean SUA was significantly higher in the cases (7.03±1.49 mg/dl) than in the controls (4.62±1.22mg/dl; P< 0.001). This showed that there was a significant rise in serum uric acid levels in patients with hypertension when compared to normotensive controls. LVH was present in 50% of the cases and in 6% of the controls (*P*<0.001). The prevalence of microalbuminuria among the cases was 40, while it was 4% in the controls (*P*<0.001).

Prevalence of hyperuricemia was 56% among the cases and 14% among the controls (P<0.001).

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Duration of hypertension: On the basis of duration of hypertension study population was divided into 2 categories those with duration of hypertension <5 years and those with duration ≥ 5 years. Total number of patients with hypertension of duration< 5 years was 58, and with duration of hypertension ≥ 5 years, was 42.

Mean SUA in patients with hypertension ≥5 years was significantly greater as compared to those with hypertension <5 years (7.47±1.43 Vs 5.99±1.16, p<0.0001) (table 3)

MAU (ACR 30-300mg/g) was found in 19 out of 58 hypertensive cases with duration <5 years and 41 out 42 hypertensive cases with duration ≥ 5 years. (table 3)

Table: 3 Parameters according to duration of hypertension

Duration of Hypertension	Number of patients	Mean serum uric acid(mg/dl)	No of Patients with microalbuminuria
<5 years	58	5.99± 1.16	19
≥ 5 years	42	7.47 ± 1.43	41

Severity of hypertension: On the basis of severity of hypertension, study population was divided into stage 1 and stage 2 based on the JNC VII classification of hypertension. Mean SUA among those with stage 2 hypertension was significantly higher than those with stage 1 hypertension (6.77±1.58 Vs 6.04±1.30, p=0.034) (table 4)

Microalbuminuria found in 13 patients out of 27 in stage 1 hypertensive patients and 47 out of 73 in stage 2 hypertension. (table 4)

Table: 4: Parameters according to stage of hypertension

Stage of Hypertension	No. of	Mean serum uric acid(mg/dl)	No of Patients with microalbuminuria
Stage 1	27	6.04 ± 1.30	13
Stage 2	73	6.77 ± 1.58	47

Urinary albumin creatinine ratio/ microalbuminuria: ACR value 30-300mg/g (microalbuminuria) was more common among cases as compared to controls**.** 60 of cases and 7 of controls had microalbuminuria.

Out of 60 cases having microalbuminuria, 50 had raised SUA, while 10 had normal SUA. Fig-1

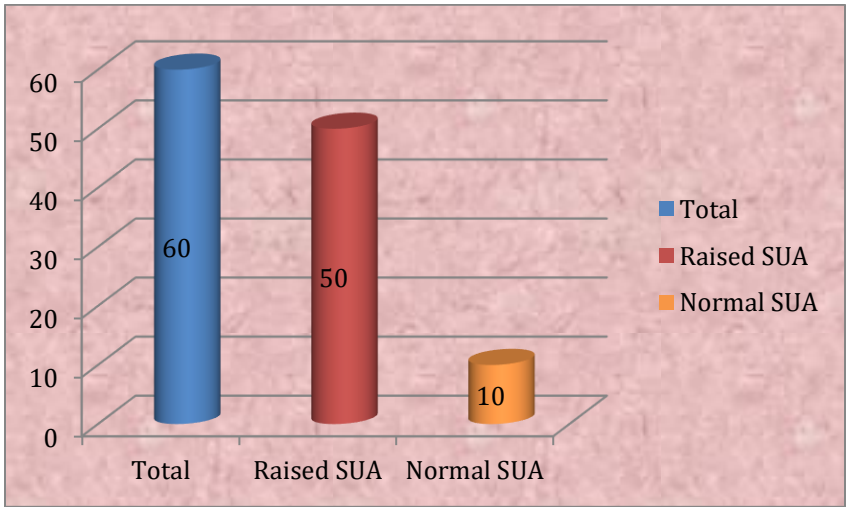

Fig 1: Association between serum uric acid and microalbuminuria

Mean serum uric acid was higher among cases with microalbuminuria as compared those without microalbuminuria(7.42±1.29 Vs 5.42±0.81, p<0.0001). (Table 5)

Table 5: Mean serum uric acid in patients with and without microalbuminuria

Catogery	No of patients	Mean SUA
Patients with MAU	60	7.42±1.29
Patients without MAU	40	5.42±0.81

Mean spot urinary albumin level in patients with hypertension ≥ 5 years was significantly higher than those with duration < 5 years (88.33±39.37 Vs 20.87±29.42, p<0.0001) Table 6, Fig 2.

Table 6: Mean MAU Levels based on Duration of Hypertension

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Duration of hypertension	Mean spot urinary albumin level (mg/L)
< 5 Years	20.87±29.42
≥ 5 Years	88.33±39.37

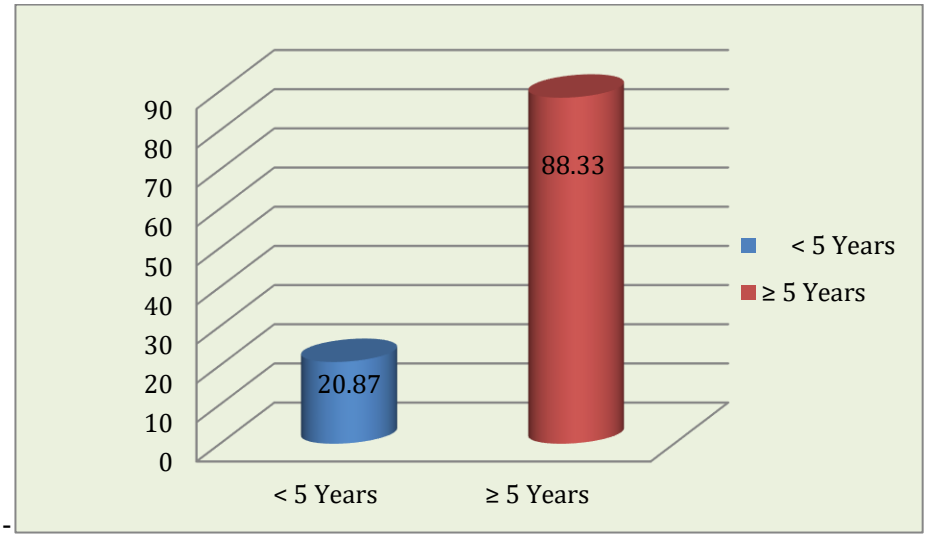

Fig 2: Mean urinary albumin levels (mg/L, y axis) based on Duration of Hypertension

SUA correlated positively with microalbuminuria among the cases (r=0.732; P<0.001), suggesting that in those with microalbuminuria, urinary albumin excretion is increased with increasing levels of SUA (Fig 12). This correlation remained significant even after controlling for the following variables: age (r=0.626; P<0.001); body mass index (BMI) (r=0.432; P=0.001); SBP (r=0.360; P=0.003); and DBP (r=0.348; P=0.003), respectively. With multiple linear regression analysis, SUA was independently associated with microalbuminuria after adjusting for confounding variables including age, BMI, SBP and DBP. The variables combined explained 70.4% of the variance observed (F- 28.540, p value <0.001). SUA made a statistically significant and unique contribution to the variance in microalbuminuria (β=0.585; P<0.001).

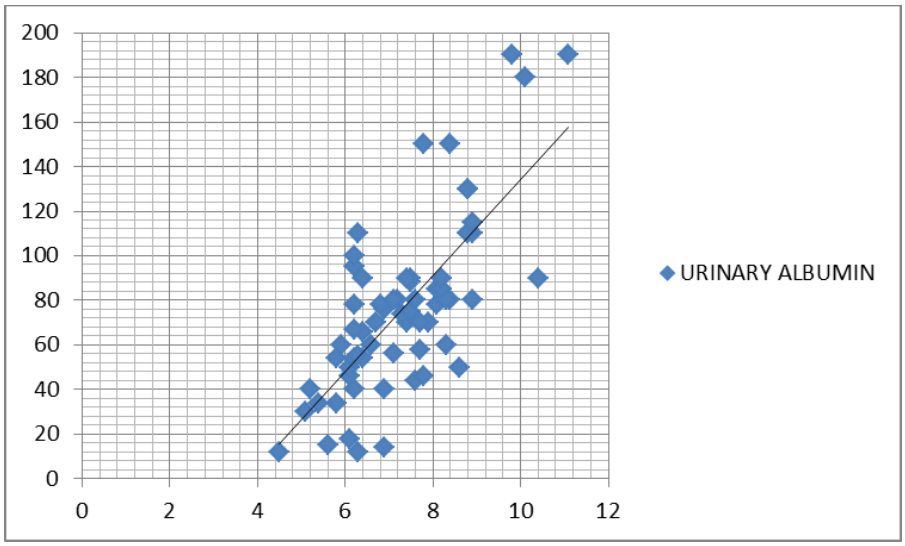

Fig 3: SUA v/s Urinary Albumin scatter plot

Left ventricular hypertrophy: LVH was present in 50% of the cases and in 6% of the controls (P<0.001), and the most common geometric pattern among the cases was concentric hypertrophy, while the majority of the controls had normal LV geometry.

Target organ damage (TOD): There was a significant positive correlation between SUA level and the number of target organs involved (r=0.255; P=0.012). This suggests that the number of TOD increased with increasing levels of SUA. Mean SUA level was higher in the cases with both microalbuminuria and LVH (7.52±0.49mg/dl), than in those with either of these indices of TOD alone (6.15±0.38mg/dl), or in those with no TOD (5.60±0.44). (table 6)

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Table 7: Mean serum uric acid and no. of Target organ damage

No. of target organ damage	Mean serum uric acid(Mean±SD)
Both TOD (MAU & LVH)	7.52±.49
Only 1 TOD(either MAU or LVH)	6.15±.38
No TOD	5.60±.44

DISCUSSION:

Uric acid, the end product of purine catabolism in humans is an anti-oxidant and has long been hypothesized that it might protect against oxidative stress or cell injury and ageing [10]. However, paradoxically the anti-oxidants can become pro-oxidant compounds in certain situations, particularly when they are present in blood at above normal levels. Current epidemiological studies have found an association between elevated SUA concentration and increased albuminuria , owing to the endothelial damage caused by SUA [11].

The main observation in this study was that hyperuricemia was more prevalent among untreated hypertensive individuals than among the normotensive controls, and elevated SUA in the patients with hypertension was accompanied by increased urinary albumin excretion.

Role of uric acid in untreated hypertensives was significant because blockade of the renin-angiotensin system by angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers which are now so commonly used in the hypertensive patients can substantially block uric acid–mediated effects[12,13,14].

Melvil R Hayden, Suresh Tyagi et al explained the potential mechanism involved in the association of hyperuricemia and hypertension as following:

1. Decreased renal blood flow (decrease glomerular filtration rate) 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 break down and increased purine (adenine and guanine) metabolism and ROS through the effect of xanthine oxidase (XO).
4. Ischemia induces increased xanthine oxidase production and increased serum uric acid and reactive oxygen species (ROS).

Our findings very well confirms to that of *Poudel et al*[15] who, in a cross-sectional study of untreated hypertensive individuals found that hyperuricemia was more common among hypertensive patients as compared to the normotensive controls (28.8% v/s 13.7%, respectively; P=0.001). However, this prevalence was lower than the 56% rate found in our study. This difference may be attributed to the higher BMI and SBP of the patients in our study.

Various other studies have also reported increased SUA levels in hypertensive patients although the prevalence data varied. *Kinsey et al*[16] in 1961 reported 46% prevalence of hyperuricemia in hypertensives. *Kolbe et al*[17] in 1965 reported 56% hyperuricemia in hypertensive patients.

Three possible conclusions can be drawn from the association of hypertension with raised SUA levels. Hypertension may arise as a result of hyperuricemia, hypertension can cause hyperuricemia and the duration and severity of hypertension is related to the SUA levels.

In the present study prevalence of hyperuricemia correlated significantly with the severity of hypertension. This correlated with both the *Kinsey et al*[16] and *Breckenridge et al*[18] studies, however *Cannon et al*[19] found that severity of hypertension had no relation to SUA level.

The significant positive correlation between microalbuminuria and SUA levels found in this study may be a result of the association between UA and risk factors for renal damage, like systolic hypertension and obesity, or due to their common link with the proinflammatory state[20]. It correlates with a study done by *Sandra n Ofori Osaretin J Odia et al*[21] on serum uric acid and target organ damage in essential hypertension who found microalbuminuria was present in 54.1% of those with hyperuricemia and in 24.6% of those with normal uric acid levels (P=0.001). This is supported by the recent findings of *Dmitriev et al*[22],who studied 100 hypertensive patients at moderate and high risk for experiencing cardiovascular events. At SUA levels 0.319 µmol/L, the hypertensive patients were found to have microalbuminuria, as well as elevated C-reactive protein (a nonspecific marker of inflammation).

Since one of the major sites of UA production in the cardiovascular system is the vessel wall, especially the endothelium, elevated UA may be a marker of endothelial dysfunction, and microalbuminuria is the renal manifestation of generalized endothelial dysfunction[23].

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It is well known that microalbuminuria is associated with an increased risk for cardiovascular disease and might be an easily detectable marker for generalized vascular dysfunction. Another finding from this study suggests that serum uric acid level can be a strong predictor of cardiovascular disease when combined with elevated blood pressure (even mildly elevated).

In clinical practice today, we rarely think of measuring uric acid as a risk factor of cardiovascular disease, not to say as a risk factor of abnormal albuminuria. Because hyperuricemia is so common and since it is relatively easy to lower uric acid levels with medications, this study suggested that not only the importance of uric acid as a risk factor for cardiovascular disease should be reconsidered, its pathogenic role in other clinical manifestations such as renal injury and increased urinary albumin excretion rate is worthy of further investigation.

Conclusion:

The study clearly demonstrates a direct correlation between serum uric acid and microalbuminuria (ACR) among untreated hypertensive patients. Severity and duration of hypertension have shown significant impact on SUA levels. SUA correlated positively with microalbuminuria among the cases suggesting that in those with microalbuminuria urine albumin excretion increased with increasing levels of SUA. In drug naive hypertensive patients, microalbuminuria was influenced by duration as well as severity of hypertension in a linear fashion.

Hyperuricemia is significantly associated with left ventricular hypertrophy, which is used as indices of cardiac end organ damage.
So hyperuricemia is strong predictor of major target organ damage (microalbuminuria and LVH)
In a setting of large population with limited resources and financial constraints, SUA can prove an effective tool in predicting future complications of hypertension even at initial stages with reasonable reliability. In common practice clinician should make it an essential part of screening schedule of hypertensive patients.

Bibliography :

1. Carretero OA, Oparil S (January 2000). "Essential hypertension Part I: definition and etiology" Circulation. 101(3): 329–35 doi:10.1161/01.CIR.101.3.329 PMID 10645931 Retrieved 2009-06-05.
2. Oparil S, Zaman MA, Calhoun DA (November 2003) "Pathogenesis of hypertension" Ann. Intern Med. 139 (9): 761–76. doi:10.7326/0003-4819-139-9-200311040-00011 PMID 14597461.
3. Hall, John E.; Guyton, Arthur C. (2006).Textbook of medical physiology. St. Louis, Mo: Elsevier Saunders. p 228ISBN 978-0-7216-0240-0.
4. "Hypertension: eMedicine Nephrology"Retrieved 2009-06-05.
5. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. N Engl J Med. 1966; 275(9):457–464.
6. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens. 2003;21(6):1011–1053.
7. Duffy WB, Senekjian HO, Knight TF, Weinman EJ. Management of asymptomatic hyperuricemia. JAMA. 1981;246(19):2215–2216.
8. Duran M, Kalay N, Ardic I, Yarlioglues M, Kayaalti F, Yilmaz Y, et al. Microalbuminuria is not associated with endothelial dysfunction and coronary atherosclerosis in patients with acute coronary syndromes. Ren Fail. 2010;32:659–65.
9. Agarwal B, Berger A, Wolf K, Luft FC. Microalbuminuria screening by reagent strip predicts cardiovascular risk in hypertension.J Hypertens. 1996;14:233-238.
10. Lippi G MM, Franchini M, Favaloro EJ, Targher G. The paradoxical relationship between serum uric acid and cardiovascular disease. Clin Chim Acta., 2008; 392: 1–7.
11. Kim SY GJ, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and metaanalysis. Arthritis Rheum., 2009; 61: 885–92.
12. MAZZALI M, HUGHES J, KIM YG, et al: Elevated uric acid increases blood pressure in the rat by an ovel crystal-independent mechanism. Hypertension 38:1101–1106, 2002
13. MAZZALI M,KANELLIS J,HAN L,et al:Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 282:F991–F997, 2002
14. NAKAGAWA T, MAZZALI M, KANG DH, et al: Hyperuricemia causes glomerular hypertrophy in the rat. Am J Nephrol 23: 2–7, 2003
15. Poudel B, Yadav BK, Kumar A, Jha B, Raut KB. Serum uric acid level in newly diagnosed essential hypertension in a Nepalese population: a hospital based cross sectional study. Asian Pac J Trop Biomed. 2014;4(1):59–64.
16. Kinsey D; Walther R; Wise HS and Smithwick R. “Incidence of hyperuricemia in 400 hypertensive patients” Circulation, 1961, 24:972.
17. Kolbe F; Gregorova I; Souka J. “Serum uric acid in hypertensives”, Lanct 1965, 1;519.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 11, 2024

18. A Breckenridge “Hypertension and Hyperuricemia” The Lancet 1966; 287; 15-18.
19. Canon P.J; Stason W.B; Demartini F.E; J.H; Sommers SC “Hyperuricemia in primary and renal hypertension” New England Journal of Medicine 1966; 275: 457-464.
20. Tsioufis C, Chatzis D, Vezali E, et al. The controversial role of serum uric acid in essential hypertension: relationships with indices of target organ damage. J Hum Hypertens. 2005;19(3):211–217.
21. Sandra N Ofori, Osarefin J Odia “Serum uric acid and target organ damage in essential hypertension” . Dove Press Journal Vascular Health and Risk Management. 2014: 10 253-261.
22. Dmitriev VA, Oshchepkova EV, Titov BN, et al. [Is there an association of uric acid level with preclinical target organ damage in moderate- and high-risk hypertensive patients?]. Ter Arkh. 2013;85(9):52–57. Russian.
23. Niskanen LK, Laaksonen DE, Nyyssönen K, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med. 2004;164(14): 1546–1551.