Original
ISSN 2521-8492

Assessment of Serum Uric Acid Level in Patients with Systemic Arterial Hypertension

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(Submitted: 08 July 2022 – Revised version received: 21 July 2022 – Accepted: 03 August 2022 – Published online: 26 December 2022)

Abstract
Objectives: To study the association between elevated serum uric acid and systemic arterial hypertension.
Methods: This study is a case-control study conducted in Al-Sadr Teaching City / Al-Najaf city from December 2019 till the end of February 2020, and included (69) cases diagnosed with systemic arterial hypertension and (71) non- hypertensive. All participants underwent anthropometric measurements and laboratory investigations for serum uric acid level, total cholesterol, high-density lipoprotein level, triglyceride level, serum blood urea and serum creatinine.
Results: The study enrolled a total of (140) participants whose mean age was (47.21 ± 12.53) years. Males comprised (57.14%) of total study sample. Serum uric acid level was found to be significantly higher among hypertensive compared to non-hypertensive, *P*-value = 0.003. Hyperuricemia was found to be significantly correlated with hypertension, with *P*-value of 0.017, Odds ratio = 9.18 (95% C.I.: 1.12 – 75.50).
Conclusions: Serum uric acid level is significantly higher in hypertensive group compared to non-hypertensive group, with the presence of significant numbers with hyperuricemia among hypertensive patients.
Keywords: Serum, uric acid, hypertension

Introduction

Uric acid is the end product of purines metabolic breakdown, and synthesized in liver, intestines, kidneys, muscles, as well as in vascular endothelium. It is also formed endogenously when intracellular nucleic acids (adenine and guanine) are released upon cellular death and metabolized.[1,2]

Adenine and guanine are converted through deamination and dephosphorylation into inosine and guanosine, respectively. Then they undergo a sequence of enzymatic conversions to eventually form xanthine, which is then oxidized into uric acid by xanthine oxidase enzyme.[3,4]

Regarding the clearance of uric acid from the body, two main routes of excretion exist: the first route, which constitutes more than 60% of uric acid excretion, is achieved by urinary excretion which is mediated by the renal system through a series of complicated processes that involve certain ion transporters that have different roles in re-absorption and secretion of uric acid within the proximal tubule of the kidneys and the second route is intestinal excretion of uric acid.[5–7]

Hyperuricemia is the condition which is characterized by abnormal elevation of serum uric acid level, which is defined by serum concentration of uric acid of more than 6.8 mg/dL.[8] Hyperuricemia has long been observed to be associated with certain diseases including hypertension, chronic renal disease, coronary heart disease, peripheral vascular disease, stroke, congestive heart failure, obesity, and metabolic syndrome.[9]

Hyperuricemia is regarded as an important public health issue due to its progressively increasing prevalence worldwide, reaching up to 20% in general population.[10,11] In the United States of America, the prevalence of hyperuricemia among general population exceeds 20%,[12] while it reaches up to 25% in China.[13] In Australia, the overall prevalence of hyperuricemia was reported to be 16.6%.[14] This high prevalence in various populations contributes significantly to increased risk of morbidity and mortality.[15]

Higher levels of serum uric acid are generally observed with increasing age, and are attributed to either higher synthesis, lower excretion, or both.[16–18] Synthesis of uric acid is controlled by the liver, which regulates the conversion of endogenous nucleo-proteins and exogenous dietary purine sources into uric acid. On the other hand, the renal system controls the excretion of uric acid from the body via certain urine-forming factors, including renal plasma flow, glomerular filtration, as well as tubular exchange.[18]

Dietary influence on serum uric acid level has long been suggested.[19] A recent study had demonstrated that the influence of dietary intake on serum level of uric acid is determined by gender and race. It was found that oral fructose consumption increase serum uric acid through the utilization of hepatic ATP in the phosphorylation and production of ADP. Alcohol intake was also found to increase hepatic production of uric acid through ATP degradation, with the added effect of dehydration and metabolic acidosis, both of which lead to reduction in urinary excretion of uric acid.[20]

Vitamin C has been suggested to have inverse influence on serum uric acid level. Higher levels of vitamin C are found to pose uricosuric effect that enhances higher fractional renal clearance of uric acid, with reduction in cellular oxidative damage that reduce the level of serum uric acid.[21] Consumption of diary products was also suggested to lower serum uric acid level, mainly due to the effect of orotic acid (present in milk) in the enhancement of the renal excretion of uric acid, as well as to the uricosuric effect of certain milk components such as casein and lactalbumin.[22]

Hypertension is defined as "long-term medical condition characterized by persistently elevated blood pressure (BP) in the arterial vessels". It is a complicated disease that affects more than one-quarter of the people, with significant morbidity and mortality.[23] Systolic blood pressure equal and higher than 130 mmHg or diastolic blood pressure equal and

higher than 80 mmHg indicate hypertension. Two stages of hypertension are defined:[24]

- Stage 1: systolic blood pressure 130–139 mmHg or diastolic blood pressure 80–89 mmHg.
- Stage 2: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

The association between hyperuricemia and hypertension had long been observed.[25] Hyperuricemia has been identified as an independent risk factor for the development of hypertension.[26,27] However, the direct causality between hyperuricemia and hypertension is still debatable, partly owing to the complicated and multi-factorial etiology of hypertension, and to the presence of multiple confounding factors among patients with hypertension.[28] This study aimed to investigate the association between elevated serum uric acid and systemic arterial hypertension.

Patients and Methods

Study Design, Setting, and Time

This study is a case-control study conducted in Al-Sadr Teaching City, An-Najaf, Iraq from December 2019 till the end of February 2020.

Study Population

The study included patients diagnosed with systemic arterial hypertension as hypertensive group and a similar numbers of normotensive individuals as non-hypertensive group.

Exclusion Criteria

Patients with the following criteria were excluded from the study:

- Chronic kidney disease.
- Patients younger than 18 years.
- Patients taking diuretics like thiazide and loop, allopurinol, chemotherapy, non-steroidal anti-inflammatory drugs.
- Myeloproliferative diseases.
- Hemolytic diseases.
- Psoriasis.
- Patients who refused to participate.

Data Collection Tools

Data was collected using a specially designed questionnaire that included diabetes mellitus, IHD, smoking, alcohol and family history of hypertension. Demographic characteristics, anthropometric measurement (body-mass index) as well as laboratory investigations including serum uric acid level, total cholesterol, high-density lipoprotein level, and triglyceride (from a fasting venous sample). All the participants in the study were fast at least 8 hours before a blood sample was withdrawn (1 mL). Blood pressure measurement was done using mercury sphygmomanometer (MDF 800) with an adequate cuff size. Participants were resting for at least 5 minutes before taken blood pressure. Systolic blood pressure was observed first heard sound (korotkoff). Diastolic blood pressure was observed at the level when the sound just muffled or disappeared.

The blood was put in tubes without anti-coagulant and transferred to biochemistry unit of laboratory, where the blood centrifuged at 2000-2500 xg for 5 minutes, to separate the serum. Then the serum put in automatic device to measure the uric acid, total cholesterol, triglyceride and HDL-cholesterol automatically. The result appeared in an adjacent screen. The name of the device is (BECKMAN COULTER AU480) and show in a picture below:

TABLE 207-1 CLASSIFICATION OF OVERWEIGHT AND OBESITY BY BODY MASS INDEX (BMI)

	OBESITY CLASS	BMI (kg/m²)
Underweight		<18.5
Normal		18.5-24.9
Overweight		25.0-29.9
Obesity	I	30.0-34.9
Obesity	II	35.0-39.9
Extreme obesity	III	≥40

From Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol.* 2014;63:2985-3023.

Statistical Analysis

SPSS® Software (version 23.0 for Linux®) was used to perform statistical analysis. Qualitative data are presented as numbers and percentages, while continuous numerical data are presented as mean ± standard deviation. *P*-value of < 0.05 was considered statistically significant. Also used *t*-test, odds ratio, confidence interval and regression control.

Ethical and Administrative Arrangements

1. Permissions were obtained from the Iraqi board for medical specialties and Al-Sadr Teaching City before conducting the study.
2. Informed verbal consent was acquired from the participants before the examination, after explaining the aim of this study and describing the data needed for acquisition for the present study.
3. All data were handled with confidentiality during collection, processing, and analysis.

Results

The study included a total of (140) participants divided into two groups: Patients group comprised of (69) diagnosed with systemic arterial hypertension (cases) and (71) normotensive individuals comprising non-hypertensive (control) group. Demographic characteristics of study groups are detailed in Table 1.

More than three-quarters (78.57%) of study participants were residents of urban places, while the remaining (21.43%) were residents of rural places.

Age of participants ranged from (21-90) years, with a mean age of (47.21 ± 12.53) years and a median age of (48.5)

Table 1. **Demographic characteristics of study groups**

Characteristics	Group			*P*-value
	Hypertensive (*n* = 69)	Non-hypertensive (*n* = 71)	Total (*n* = 140)	
Age (mean ± SD)	52.2 ± 11.8	42.3 ± 11.2	47.2 ± 12.5	**< 0.001***
Gender				
Male	33 (41.25%)	47 (58.75%)	80 (100%)	**0.028***
Female	36 (60.00%)	24 (40.00%)	60 (100%)	
Residence				
Urban	54 (49.09%)	56 (50.91%)	110 (100%)	0.930
Rural	15 (50.00%)	15 (50.00%)	30 (100%)	
BMI (mean ± SD)	28.0 ± 3.6	26.6 ± 2.6	27.3 ± 3.2	**0.010***
History of DM	23 (33.33%)	6 (8.45%)	29 (20.71%)	**<0.001***
History of IHD	11 (15.94%)	1 (1.41%)	12 (8.57%)	**0.002**
Family History of HT	44 (63.77%)	37 (52.11%)	81 (57.86%)	0.163
Smoking	21 (30.43%)	28 (39.44%)	49 (35.00%)	0.264
Alcohol	2 (2.90%)	1 (1.41%)	3 (2.14%)	0.617[F]

*Significant at $P < 0.05$. [F]Calculated using Fisher exact test.

years. Age group distribution of study groups is presented in Figure 1.

Males formed (57.14%) of the study participants, while females formed the remaining (42.86%), as illustrated in Figure 2.

Duration of hypertension ranged from two months up to (40) years, with a median duration of (3) years, as illustrated in Figure 3.

More of hypertensive group had duration less than 5 years as shown in Table 2.

(35%) of hypertensive and (37%) of non-hypertensive had BMI of overweight (25-29.9). BMI classes of study participants are illustrated in Figure 4.

Serum uric acid level was found to be significantly higher among hypertensive compared to non-hypertensive (Table 3). Mean difference between the two groups was (0.61) mg/dL.

Among male participants, hypertensive patients had significantly higher uric acid level compared to non-hypertensive. Similarly, female with hypertension had significantly higher uric acid level compared to non-hypertensive female (Table 4).

Regarding hyperuricemia, a total of (9) patients had uric acid level higher than 6.8 mg/dL, constituting (6.43%) of total study participants. Proportion of patients with hyperuricemia was found to be significantly higher among hypertensive compared to non-hypertensive (Table 5).

Odds ratio for patients with hyperuricemia to develop hypertension was found to be 9.18 (95% C.I.: 1.12 – 75.50).

No significant correlation was observed between uric acid and neither of age, BMI or duration of hypertension (*P*-value > 0.05) (Table 6).

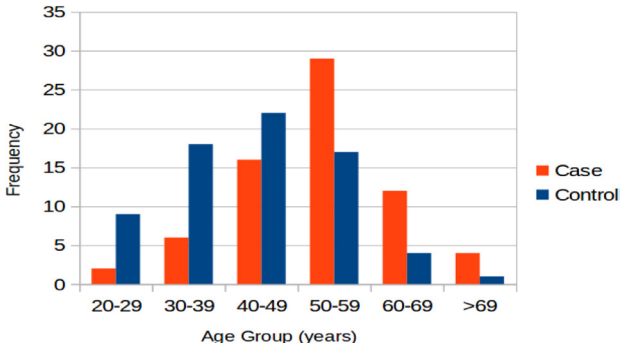

Fig. 1 **Age group distribution of study groups.**

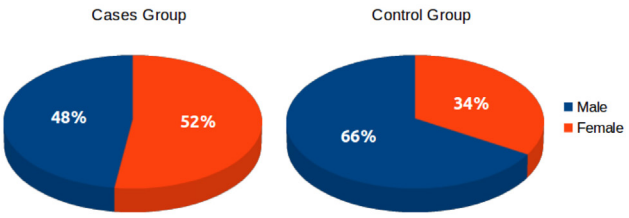

Fig. 2 **Gender distribution of study groups.**

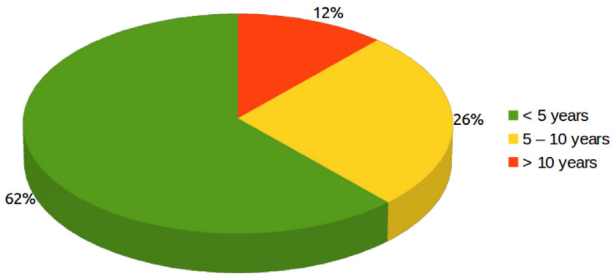

Fig. 3 **Hypertension duration among hypertensive participants.**

Table 2. **Frequency distribution of duration of hypertension among hypertensive group**

Variable		Frequency	Percentage
Duration of Hypertension	< 5 years	43	61.76%
	5 – 10 years	18	26.47%
	> 10 years	8	11.76%

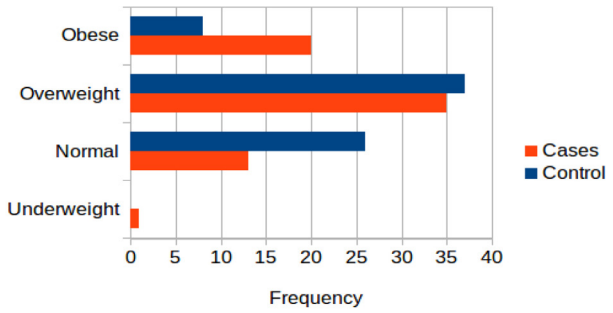

Fig. 4 **BMI classes of study groups.**

Within hypertensive group, no significant correlation was observed between serum uric acid and either of total cholesterol, HDL and triglyceride (Table 7).

Regarding degree of hypertension, no significant difference in serum uric acid was observed between hypertensive with stage 1 hypertension (5.19 ± 1.29) and stage II hypertension (5.15 ± 1.39), Student's *t*-test = 0.13, *P*-value = 0.901. Similarly, no significant correlation was observed between hyperuricemia and stage of hypertension (Table 8).

A multiple linear regression was calculated to predict serum uric acid level based on hypertension, age, gender, BMI, and smoking status. Only hypertension was found to be a significant predictor for serum uric acid level (*P*-value = 0.005). Each of age, gender, BMI, and smoking status were non-significant predictors (*P*-value > 0.05, Table 9).

Table 3. **Comparison between hypertensive and non-hypertensive regarding serum uric acid level**

Group	Serum uric acid level (mg/dL)			*P*-value
	Mean	SD	Range	
Hypertensive (*n* = 69)	5.17	1.34	2.20 – 9.50	
Non-hypertensive (*n* = 71)	4.56	0.98	2.10 – 7.00	**0.003***
Total (*n* = 140)	4.86	1.20	2.10 – 9.50	

*Significant at *P* < 0.05.

Table 4. **Comparison between hypertensive and non-hypertensive regarding serum uric acid level by gender**

Group	Serum uric acid level (mg/dL)			
	Males		Females	
	Mean ± SD	*P*-value	Mean ± SD	*P*-value
Hypertensive (*n* = 33)	5.34 ± 1.31		5.01 ± 1.36	
Non-hypertensive (*n* = 47)	4.76 ± 0.91	0.0219*	4.18 ± 1.02	0.0138*
Total (*n* = 80)	5.00 ± 1.12		4.68 ± 1.29	

*Significant at *P* < 0.05.

Table 5. **Hyperuricemia status by study group**

Group	Hyperuricemia (uric acid > 6.8 mg/dL)			*P*-value
	Present	Not present	Total	
Hypertensive	8 (11.59%)	61 (88.41%)	69 (100%)	
Non-hypertensive	1 (1.41%)	70 (98.59%)	71 (100%)	**0.017***
Total	9 (6.43%)	131 (93.57%	140 (100%)	

*Significant at P < 0.05.

Table 6. **Correlation between serum uric acid and certain variables within hypertensive group**

Variables	Correlation with serum uric acid	
	Correlation Coefficient	*P*-value
Age	< 0.01	0.996
BMI	–0.13	0.303
Duration of HT	0.06	0.647

Table 7. **Correlation between serum uric acid and lipid profile within hypertensive group**

Variables	Correlation with serum uric acid	
	Correlation Coefficient	*P*-value
Total cholesterol	0.15	0.206
HDL	–0.02	0.872
Triglycerides	0.13	0.296

Discussion

Hyperuricemia is an important public health issue as its prevalence reaches up to 20% in general population.[10,11] In this study conducted in AL-Sadr Teaching City/AL-Najaf city, Iraq included (140) participants and the number of the participants were consistent with other studies such as Raina et al. included (100) participants[29] and El-Yassin et al. included (130) participants.[30] Regarding the median age of the participants in the current study was 48.5 years, higher than the median age of

Table 8. **Hyperuricemia status by stage of hypertension among hypertensive group**

Stage of Hypertension	Hyperuricemia (uric acid > 6.8 mg/dL)			*P*-value
	Present	Not present	Total	
Stage I	3 (10.71%)	25 (89.29%)	28 (100%)	
Stage II	5 (12.20%)	36 (87.80%)	41 (100%)	0.850
Total	8 (11.59%)	61 (88.41%)	69 (100%)	

*Significant at *P* < 0.05.

Table 9. **Multiple linear regression analysis for certain factors as predictors of serum uric acid level**

Factor	Predictor *P*-value
Hypertension (Case vs. Control)	**0.005***
Age (years)	0.386
Gender (Male vs Female)	0.108
BMI (kg/m^2)	0.795
Smoking status	0.468

*Significant at *P* < 0.05.

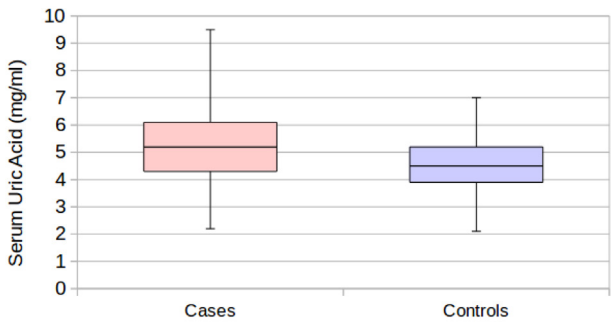

Fig. 5 **Whisker boxplot showing serum uric acid among study groups.**

the participants in Poudel et al. which was 44 years.[31] The difference related to the range of age in current study (21-90) years while in Poudel et al. was (16-65) years.

As in shown in Table 1; regarding history of diabetes mellitus and ischemic heart disease in the current study, there were significant difference between hypertensive and non-hypertensive which was agreement by Raina et al.,[29] and El-Yassin et al.[30] Insulin resistant individuals secrete larger amounts of insulin in order to maintain an adequate glucose metabolism. The kidney was responded to these elevated insulin levels by decrease uric acid clearance, probably linked to insulin induced urinary sodium retention.[32] Insulin resistance may elevated blood pressure directly via enhanced proximal tubular sodium reabsorption[33] or indirectly via sympatho-adrenal system.[34] Elevated uric acid levels were suggested to trigger the development of arteriosclerosis through the oxidate stress posed by the production of UA and the facilitation of arteriosclerosis by the effect of monosodium urate crystals that were present in cases of hyperuricemia. These changes were believed to be associated with hypertension as well as coronary artery disease.[35] Also regarding BMI, was statistically significant difference between hypertensive and non-hypertensive in current study with agreement by Poudel et al.,[31] and not agree by Raina et al.[29] Although uric acid had the anti-oxidant effects, it was appeared a strong oxidant properties in obesity.[36] Both the oxidative stress due to uric acid and inflammation in obesity may influence the patient to increase the risk for HT. While, history of the smoking had statistically not significant in this study as with Raina et al.[29] and Poudel et al.[31] The result of chronic exposure to the smoking that was an important source of oxidative stress lead to the reduction in the production of uric acid endogenously.[37] Regarding the history of alcohol intake in the present study shown statistically not significant, which inconsistent by Perlstein et al.[38] Alcohol is a source of purines. These compounds produced uric acid when broken down by the body. Alcohol increase the metabolism of nucleotides. These were an additional source of purines that can be turned into uric acid.[39]

Serum uric acid level in hypertensive patients had statistically significant as shown in Table 3; this result was supported by Raina et al.[29] Elevated uric acid levels were suggested to trigger the development of arteriosclerosis through the oxidate stress posed by the production of UA and the facilitation of arteriosclerosis by the effect of monosodium urate crystals that were present in cases of hyperuricemia. These changes were believed to be associated with hypertension as well as coronary artery disease.[35]

The comparison between hypertensive and non-hypertensive in the present study had revealed that difference in uric acid level regarding gender. The *p*-value of uric acid level between male hypertensive and male non-hypertensive in the present study was (0.021) while in females it was (0.013) as shown in Table 4. These findings were inconsistent by Raina et al.,[29] however, in their study revealed that the *P*-value (0.01) between male cases and male control, while in females it was (0.46). More females in the present study beyond reproductive age group while in Raina et al., more females within the reproductive age and uricosuric effect of estrogen may be the reason.[29]

The current study had shown that (11.59%) of hypertensive had hyperuricemia compared to (1.41%) of non-hypertensive. These findings were comparable to the findings by El-Yassin et al. shown (11%) of cases had hyperuricemia while (9%) of control had hyperuricemia.[30]

In the present study shown patients with hyperuricemia were with odds ratio of 9.18 (95% C.I.: 1.12 – 75.50) as in Table 5. These findings were inconsistent with Poudel et al., in their study patients with an odds ratio of 2.56 (95% C.I.: 1.55-4.21).[31] This discrepancy could be due to sample size between the current study (140 participants) and Poudel et al. study (410 participants). This interpretation was supported by the odds ratio reported by Raina et al. in their study which included 100 participants, which was equal to 4.9 (95% C.I.: 1.3 – 18.8).[29]

Regarding the correlation between serum uric acid and total cholesterol, triglyceride and HDL in the present study shown no statistically significant as in Table 7; with agreement by Raina et al.[29] These findings in the current study were inconsistent by Poudel et al.[31] and El-Yassin et al.,[30] which shown significant statistically. Hyperuricemia was considered to be a mediator of the proinflammatory endocrine imbalance in the adipose tissue which may be one of the important factors of dyslipidemia and the inflammatory process that leads to atherogenesis.[40] When establish the diagnosis of hyperuricemia, clinical suspicion of coexistent dyslipidemia should be required. These abnormalities had a close relationship to coronary artery disease. Detection and treatment of disordered lipid and uric acid metabolisms in patients with other risk factors for cardiovascular disease should be given a high priority.[41] The specific mechanism of increase serum triglyceride and uric acid had not been elucidated. Some studies suggested that may be due to disorder of free fatty acids metabolism caused by triglyceride, as the increase of triglyceride lead to increase free fatty acid production. Accelerating the decomposition of adenosine triphosphate, which lead to increase in uric acid.[42]

In the present study, no significant correlation was observed between the stage of hypertension and uric acid level as shown in Table 8. Mean serum uric acid among patients with stage 1 hypertension was (5.19) mg/dL, which was closely similar to the value of (5.37) mg/dL reported by Neki and Tamilmani. However, serum uric acid level was significantly higher among patients with stage 2 hypertension, with a mean of (6.39) mg/dL.[43] This finding contrasted with the finding by the present study, which could be attributed to the variation in the type and extent of hypertension-related complications that exist in patients with stage 2 hypertension, and the role of such complications as confounding factors in elevating serum uric acid level.

Conclusion

This study concludes that serum uric acid level is significantly higher in hypertensive group compared to non-hypertensive group, with the presence of significant numbers with hyperuricemia among hypertension patients.

Conflict of Interest

None.

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