

Does Hypertension Contribute to Eliciting Gout Symptoms in Hyperuricemic Patients?

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ABSTRACT

Background and objective: Treatment of gout flares with uric acid-lowering medications is not optimal in hypertensive hyperuricemic patients and only sedates gout symptoms. The current study aimed to explore whether blood pressure control (BP) determines the symptomatic or asymptomatic status of hyperuricemic patients with elevated blood pressure.

Patients and Methods: A cross-sectional study was conducted with 211 hypertensive hyperuricemic participants obtained from the King Saud Medical City (KSMC). All patients were categorized into three blood pressure groups: controlled, uncontrolled, and untreated hypertension groups. Based on uric acid (UA) levels, the participants were divided into three UA tertiles: T1, <157 $\mu\text{mol/L}$, T2:157-360 $\mu\text{mol/L}$ and T3:>360 $\mu\text{mol/L}$. Descriptive statistics of the study variables and multivariate regression analysis were utilized to determine the association between gout joint flares and blood pressure after adjustment of the risk factors.

Results: The findings revealed an increased prevalence of gout symptoms across the three BP groups. Moreover, this association was significant even after adjustment of the age, gender, BMI, and smoking. Also, there was a significant gout-symptoms difference when comparing the corresponding UA tertiles in each blood pressure group. Moreover, a significant positive association existed between blood pressure and the frequency and number of gouty attacks. The more controlled blood pressure, the less frequent and short-duration attacks.

Conclusion: Hypertension was strongly suggested as a major risk factor in eliciting gout symptoms in hyperuricemic patients, whatever is the level of serum uric acid.

Keywords: Blood pressure, Gout, Symptomatic hyperuricemia, Serum uric acid level.

INTRODUCTION

Enhanced living conditions and good life standards are linked to metabolic syndrome development in many individuals, a major risk factor for cardiovascular diseases. Both hyperuricemia and hypertension (HTN) are eminent components of the metabolic syndrome. Elevated serum uric acid (UA) is recently proposed as a risk factor for HTN ⁽¹⁾. The relation between serum UA and the incidence of HTN has got a wide-scale attention in the last few years and were greatly investigated ⁽²⁾.

Several epidemiological studies ^(3,4) have proven a positive serum UA/hypertension association. Taken in consideration the dietary life style, both might coexist together, as comorbidities in metabolic syndrome ⁽⁵⁾, meanwhile other studies showed that serum UA could induce HTN via rising renal renin, reducing nitric oxide release, and increasing oxidative stress leading to vascular vasoconstriction and elevated blood pressure ⁽²⁾. Moreover, 2 meta-analysis studies ^(6,7) suggested a major effect of UA-lowering therapies on blood pressure, which further confirms the significant serum UA/HTN

relationship. On the opposite, a Chinese study ⁽⁸⁾ reported that HTN could induce hyperuricemia and the co-association of hyperlipidemia is much powerful in serum UA elevation.

Hypertension is a worldwide health problem and is considered as one of the crucial causes of heart diseases and other life-threatening complications ⁽⁹⁾. In the Kingdom of Saudi Arabia (KSA), about 27.1% of Saudi individuals suffer from both HTN and hyperuricemia, and the latter could be symptomatic or asymptomatic ⁽¹⁰⁾. Mean uric acid ranges have been reported, and the frequency of hyperuricemia is significantly higher in hypertensive patients in comparison to healthy people ⁽¹¹⁾.

Based on the literature data, a cause-effect relationship has existed between serum UA and hypertension. To the best of authors' knowledge, no studies have demonstrated the association between the gout symptoms and elevated blood pressure. Therefore, the current study aimed to explore whether symptomatic hyperuricemia and clinical gout are associated with high blood pressure.

PATIENTS AND METHODS

Data sources

The research data were obtained from the national records archived by the Rheumatology Department, King Saudi Medical City (KSMC) during the period 1 September 2020 to 31 August 2022, which are a nationally representative sample of hypertensive patients with hyperuricemia in Riyadh City, Saudi Arabia. A baseline information on age, gender, uric acid levels, blood pressure (BP), medication history, number and duration of gout attacks, and gout symptoms were recorded.

Ethical statement

The study adhered to the Declaration of Helsinki during execution, and the proposal was approved by

the Institutional Review Board of King Saud Medical City, Saudi Arabia, IRB registration/protocol number: H-01-R-053, IORG0010374, H1R1-28-Mar22-02. Due to the retrospective pattern of data collection, the Institutional Review Board (IRB) waived the requirement for informed consent.

Study population

The KSMC database were surveyed for two years back for selection of the participating patients. 211 patients aged 18 years and older with hyperuricemia and hypertension (isolated systolic, diastolic HTN, or both) were enrolled in a cross-sectional study.

Of the 2,435 potential study participants, 2,224 were excluded (Figure 1).

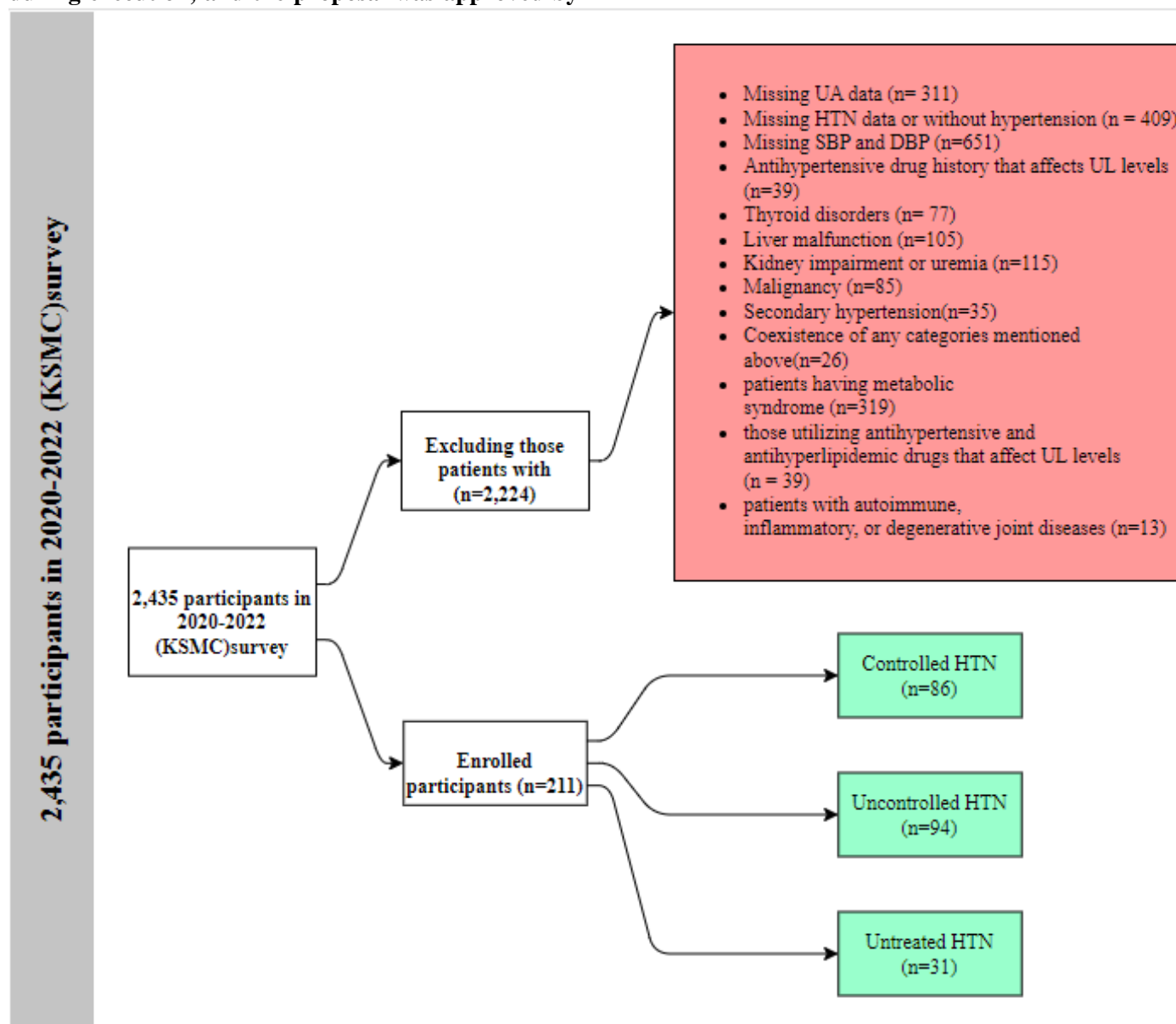


Fig. 1: Flowchart of the study design and participants excluded from the study. KSMC, King Saud Medical City; UA, uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension.

Definition of hypertension, hyperuricemia, and risk factors

In this study, the gout symptoms were the primary outcome, and BP was the exposed variable including systolic blood pressure (SBP) and diastolic blood pressure (DBP). According to the 2018 ESC/ESH (European Society of Cardiology/European Society of Hypertension) for hypertension management ⁽¹²⁾, HTN is defined as systolic blood pressure (SBP) ≥ 140 and diastolic blood pressure (DBP) ≥ 80 or as a condition when the participants are already diagnosed and currently on antihypertensive drugs. The participants were divided into three-blood pressure (BP) groups and were defined as follow: "Untreated HTN" included all participants with a BP range of $152\pm 8/88\pm 5$ and those were recently diagnosed and still not receiving HTN medications yet during last six months of the study duration. "Controlled HTN patient group" included all participants with a BP range of $122\pm 5/72\pm 6$ and those patients were on regular HTN medications during the two years of the study. "Uncontrolled HTN group" included all participants with a BP range of $145\pm 5/87\pm 7$ as they were on irregular drug intake.

In the current study, hyperuricemia is defined as a serum level of uric acid >6 mg/dL (360 $\mu\text{mol/L}$) as there is no commonly accepted definition of hyperuricemia based solely on UA level due to differences related to gender and age ⁽¹³⁾. Asymptomatic hyperuricemia is defined as current medications use for hyperuricemia or serum UA > 360 $\mu\text{mol/L}$ with no current or previous clinical gout, mainly big toe joint inflammation. Symptomatic hyperuricemia (gout) included those patients on current gout therapy or those with a serum level of uric acid >6 mg/dL (360 $\mu\text{mol/L}$) and manifested by big toe joint flares. The participants were further divided into three tertiles (T) depending on the serum UA levels obtained from the patients' medical records (T1: < 157 $\mu\text{mol/L}$, T2: 157 - 360 $\mu\text{mol/L}$, and T3: > 360 $\mu\text{mol/L}$). The first two tertile (T1 and T2) are considered normal UA level. Regarding the risk factors, current tobacco smokers were defined as those individuals who smoked in the last one year or those who stopped smoking within the last 6 months. Other data, including age, gender, and body mass index (BMI), were collected in a predetermined format. Body mass index (kg/m^2), as a marker of obesity, was calculated by dividing the individual weight in kilograms by the length (in meters) square.

Statistical analysis

All data obtained were analyzed by a biostatistics expert, using SPSS software, version 24 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Descriptive

analysis was performed, which included frequency, percent, mean and standard deviation. The data were normally distributed as initially checked by Kolmogorov and Shapiro tests. Independent student-t test and One-way ANOVA were used to detect the difference for each UA tertile among BP groups. Two-way ANOVA was used to detect the effect of two independent variables (blood pressure and the uric acid) on the dependent variable (gout symptoms). Crude and adjusted Odds ratio (OR) with 95% confidence interval for hyperuricemia and gout symptoms were measured after adjustment for age, gender, BMI, and smoking habits using multivariate regression analysis. Also, the relationship between blood pressure (SBP and DBP) and the number and duration of gouty attacks was evaluated by Pearson correlation coefficient. Statistical significance was adopted at p value less than 0.05.

RESULTS

Baseline demographic and clinical characteristics of enrolled patients

The participants' characteristics were summarized in table 1. Statistically significant age, gender, BMI differences were noted among the 3 HTN groups. The 3 HTN groups showed a noticeable increasing trend in the mean value of both SBP and DBP. The 1st UA tertile was limited to the controlled HTN group. The mean value of the 2nd UA tertile was significantly high in the uncontrolled BP group when compared to the controlled BP group. The mean value of the 3rd UA tertile was significantly higher in the untreated BP group when compared to the uncontrolled BP and controlled BP groups indicating increasing uric acid trend across the three BP groups.

Obvious variation in the distribution of UA tertiles was noted, among the BP groups. The controlled group included 7 patients (8.2%) in the 1st UA tertile, 34 patients (39.5%) in the 2nd UA tertile, and 45 participants (52.3%) in the 3rd UA tertile. The uncontrolled BP group included 8 patients (8.5%) in the 2nd UA tertile and 86 (91.5%) in the 3rd UA tertile. However, the untreated BP group included only 31 patients (100%) in the 3rd UA tertile.

Regarding the gout symptoms, the difference was significant among the 3 groups as the controlled BP group, had significantly much more asymptomatic participants than the other 2 groups. Regarding the gout flares last year, the uncontrolled and untreated BP groups had significantly much more fares compared to the controlled group, which had no attacks at all. The mean duration of the gouty flares was significantly longer in the uncontrolled and untreated BP groups compared to nil in the controlled group

Table 1: Baseline description of the included participants

	Controlled HTN	Uncontrolled HTN	Untreated HTN	p-value
Number (%)	86 (40.7%)	94 (44.6%)	31 (14.7%)	
Blood pressure (mmHg)				
SBP (mean ± SD)	121.4±2.9	145.4±3.1	151.3±5.2	<0.001
DBP (mean ± SD)	72.4±3.6	87.6±4.2	88.3±3.2	<0.001
Age, n (mean ± SD)	47.1±2.1	52.2±3.1	49.1±2	<0.001
Gender, n (%)				
Male	65 (30.8%)	87 (41.2%)	27 (12.8%)	0.001
Female	21 (10%)	7 (3.3%)	4 (1.9%)	0.001
BMI, n (mean ± SD)				
Male	65 (24.5±2.51)	87 (26.1±1.91)	27 (27±3.71)	<0.001
Female	21 (23.1±3.02)	7(26.3±1.1)	4(26.1±2.2)	<0.001
Smoking, n (%)				
Male	40/65 (61.5%)	69/87 (79.3%)	20/27 (74.1%)	
Female	5/21 (23.8%)	0/7 (0%)	1/4 (25%)	
Uric Acid (µmol/L)				
<157, n (mean ± SD)	7 (149±1.1)	-	-	
157-360, n (mean ± SD)	34 (223±3.2)	8 (315±1.5)*	-	0.005
>360, n (mean ± SD)	45 (472±2.3)	86 (511±3.2)**	31 (545±4.2)**	0.005
Gout symptoms, n (%)				
Yes	5 (5.8%)	94 (100%)	30 (96.8%)	<0.001
NO	81 (94.2%)	0 (0.0%)	1(3.2%)	
Number of gouty flares last year				
1-2	0	22(23.4%)	2(6.5%)	<0.001
3-5	0	68(72.3%)	27(87.1%)	
None	86(100%)	4(4.3%)	2(6.5%)	
Duration of gouty flares, days (mean ± SD)	0±0	7.8±1.1	8.8±1.2	<0.001

* Significant when compared with the corresponding tertile of the controlled BP group. ** Significant when compared with the corresponding tertile of the uncontrolled BP group. HTN: hypertension, SBP: systolic blood pressure, DBP: diastolic blood pressure, n: number, SD: standard deviation, BMI: body mass index.

Blood pressure groups and prevalence of the uric acid tertile

The serum UA tertiles in each BP group was presented in figure 2. The prevalence of the first UA tertile was restricted to controlled BP group. The 2nd UA tertile was restricted to the controlled and uncontrolled BP groups with a high prevalence in the controlled HTN group. The 3rd UA tertile was distributed in the 3 blood pressure groups with high prevalence in patients with elevated blood pressure. When analyzing the gout symptoms, figure 3 showed significant symptoms difference (p<0.001) between the three BP groups. The first UA tertile was asymptomatic in the controlled HTN group, meanwhile absent in the other 2 BP groups. The 2nd UA tertile was asymptomatic in the controlled group, symptomatic in the uncontrolled BP group, meanwhile absent in the untreated HTN group. The 3rd UA tertile was asymptomatic in the controlled group, meanwhile symptomatic in the other two BP groups. Collectively, the controlled HTN group included the three UA tertile patients and all were asymptomatic for gout, whatever the UA level. The uncontrolled HTN included only 2 UA tertiles (157-360 and those >360) and both were positive for gout symptoms. The untreated BP group included only one UA tertile (those > 360) and were also symptomatic for gout.

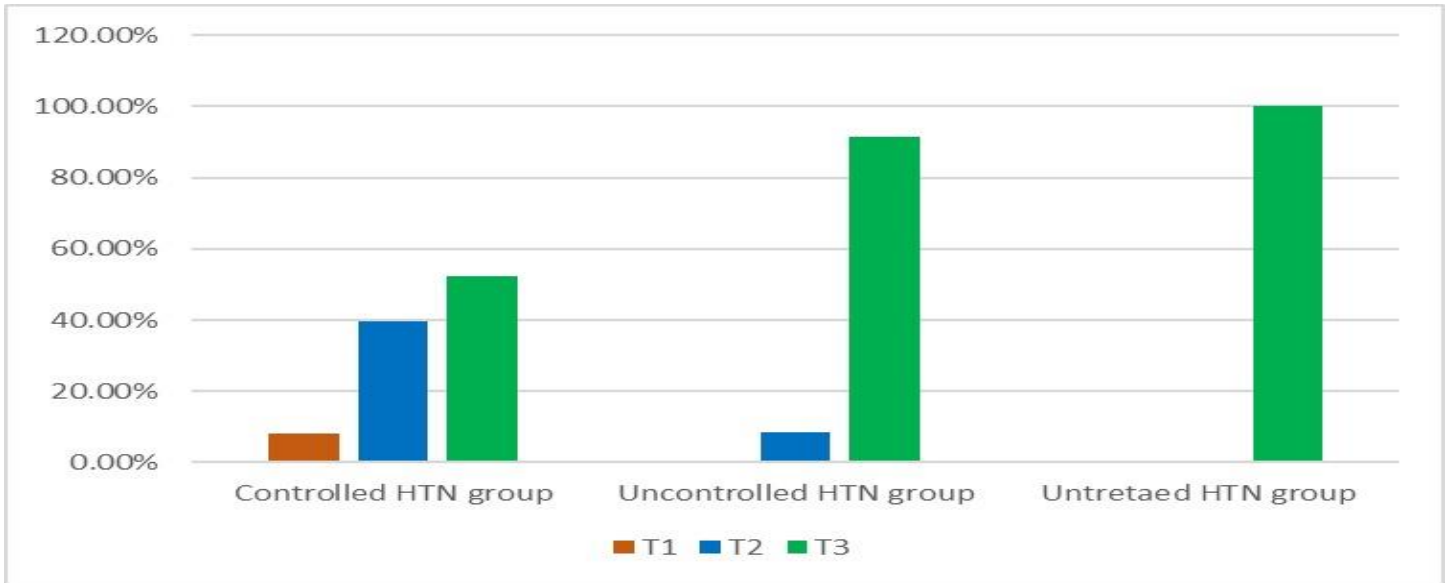


Fig. 2: Bar chart showing the prevalence of the UA tertiles across the 3 BP groups. T1:<157 μmol/L, T2:157 – 360 μmol/L, T3: >360 μmol/L.

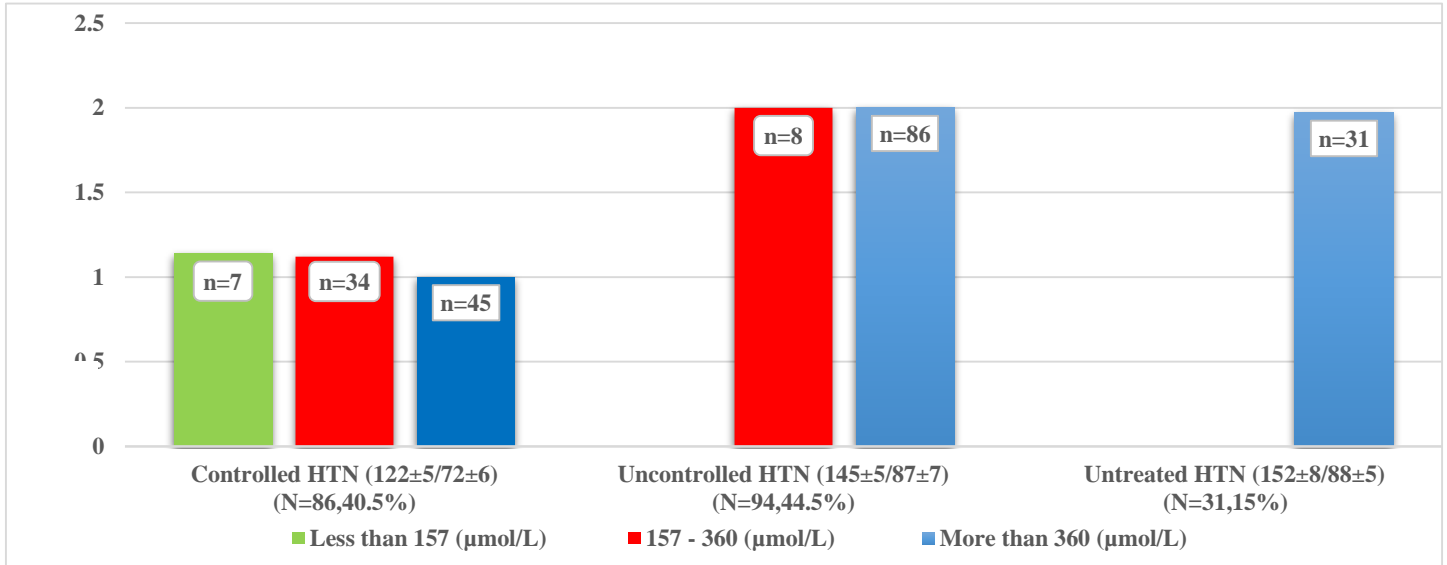


Fig. 3: Bar chart showing the effect of BP and UA tertile on gout symptoms in the 3 blood pressure groups (p<0.001).

Association of blood pressure and prevalence of hyperuricemia

Hyperuricemia (UA level > 360 μmol/L) was detected in 162 of a total 211 participants (76.8 % prevalence rate). The prevalence of hyperuricemia among the participants of each BP group was displayed in table 2. There was a gradual increase (p<0.001) in the prevalence of hyperuricemia across the BP groups being higher in patients with high BP. This association was also significant after adjustment for age, gender, BMI, and smoking habits. The Odds ratio (95% CI) were 1.4 for the uncontrolled HTN group, and 1.7 for the untreated HTN group, when compared to the control group (reference group) with p for trend < 0.01 using multivariate regression analysis (table 2)

Association of blood pressure and prevalence of gout symptoms

The prevalence of gout symptoms (clinical manifestations of gout even though normalized serum UA) in BP groups was displayed in table 2. It was 5.8% in the controlled BP group and those were normouricemic. The gout symptoms were present in all participants of the uncontrolled BP group (100%) even through 8.5% of the group participants were normouricemic. However, the untreated group showed a prevalence rate of 93.5%. There was a predominance (p<0.001) of gout symptoms in the patients’ groups with high BP. This association was also significant after adjustment for age, gender, BMI, and smoking habits. The Odds ratio (95% CI) were 1.9 for the uncontrolled HTN group, and 2.5 for the untreated HTN group, when compared to control group (reference group) with p for trend < 0.01 using multivariate regression analysis.

Table 2: Crude and adjusted Odds ratio showing the association of blood pressure and the prevalence of hyperuricemia and gout symptoms

	Blood pressure			P value for trend
	Controlled BP group (n=86)	Uncontrolled BP group (n=94)	Untreated BP group (n=31)	
Number of hyperuricemia/participants	45/86	86/94	31/31	
Prevalence	52.3%	91.5%	100%	
Crude OR (95% CI)	reference	1.5 (0.1-9.3)	1.8 (0.5-11.2)	<0.01
Adjusted OR ^a (95% CI)	reference	1.4 (0.2-10.4)	1.7 (0.6-9.8)	<0.01
Number of gout symptoms/participants	5/86	94/94	30/31	
Prevalence	5.8%	100%	96.8%	
Crude OR (95% CI)	reference	2(0.3-12.5)	2.7 (0.6-13)	<0.01
Adjusted OR ^a (95% CI)	reference	1.9 (0.2-11.1)	2.5 (0.9-17.4)	<0.01

Note: OR means Odds ratio. CI means confidence interval. ^a: OR after adjustment for age, gender, BMI, and smoking using multivariate regression analysis. Crude OR means Odds ratio with no adjustment for any risk factors.

Association of the number and duration of gouty attacks with the blood pressure

A significant positive correlation was detected between the number/duration of gouty attacks and the blood pressure (Fig. 4). Pearson’s correlation coefficient analysis revealed that the number of gout flares (last year) was significantly, and positivity associated (Fig. 4A, B) with SBP ($r = 0.853$, $p < 0.001$) and DBP ($r = 0.885$, $p < 0.001$). Also, the duration of each gout flare was significantly, and positivity associated (Fig. 4C, D) with SBP ($r = 0.841$, $p < 0.001$) and DBP ($r = 0.705$, $p < 0.001$). The more controlled SBP and DBP, the less frequent attacks and short attack duration.

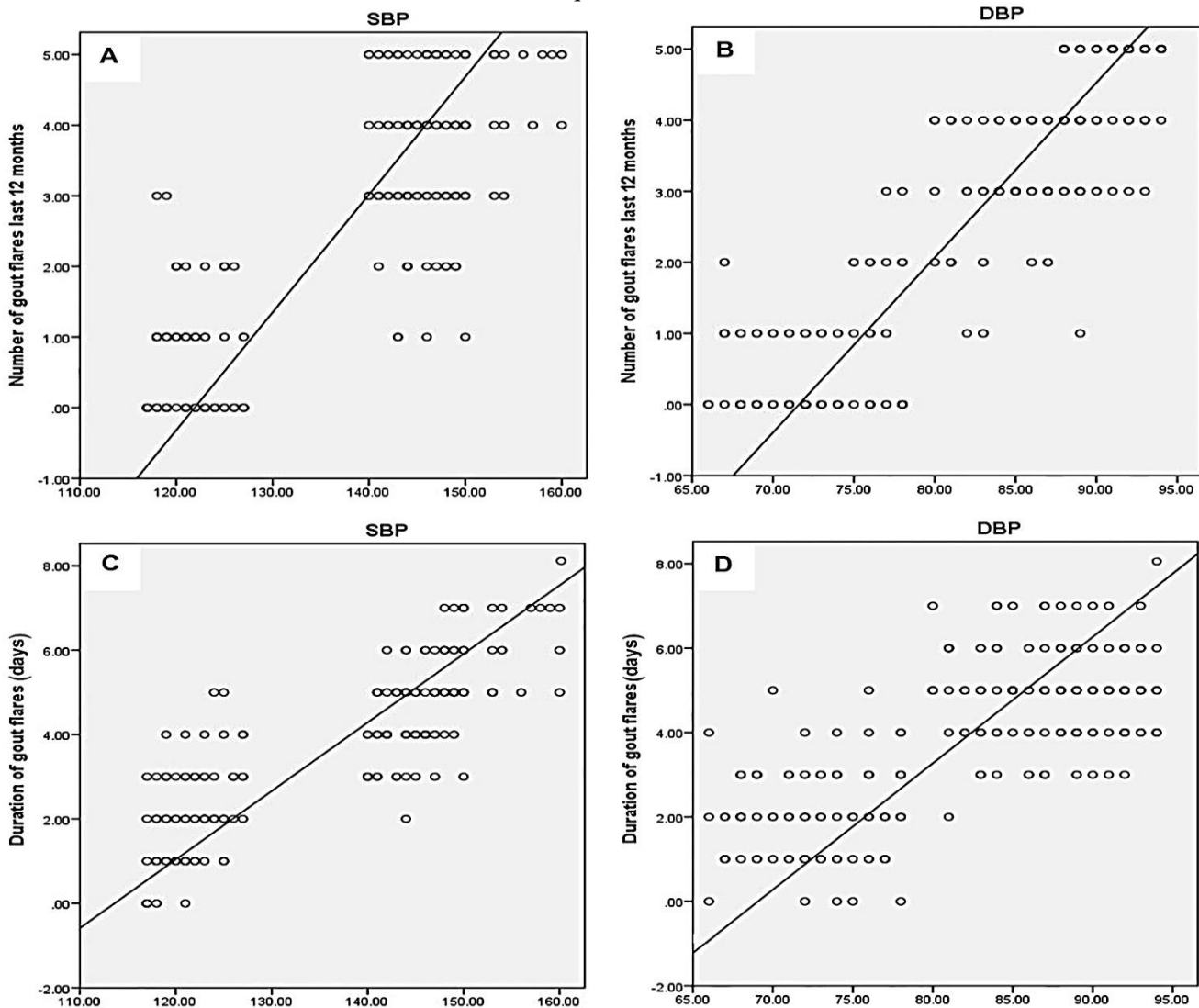


Fig 4: The association of the number (A, B) and duration (C, D) of gout flares with the blood pressure (SBP and DBP)

DISCUSSION

The current study presented a unique finding considering hypertension (HTN) as a major risk factor in eliciting the gouty symptoms in hyperuricemic patients. The study conducted a random survey of 211 hypertensive hyperuricemic participants in Riyadh City, Saudi Arabia. The participants were analyzed in three HTN groups (controlled, uncontrolled, and untreated HTN groups). All the untreated HTN participants showed high uric acid (UA) levels more than 360 $\mu\text{mol/L}$ and were symptomatic for gout having joint flares. Interestingly, all patients with controlled HTN were asymptomatic, although more than half of those patients (52.3%) showed high UA level more than 360 $\mu\text{mol/L}$.

Several epidemiological studies declared an independent correlation between serum UA levels and the occurrence of hypertension, however actual causality is not yet clear⁽¹⁴⁾. Renin angiotensin activation, endothelial malfunction, renal afferent arteriopathy, generalized inflammation, and oxidative stress are suggested pathophysiological mechanisms explaining the role of UA in HTN development⁽¹⁵⁾.

In their latest review, **Yip et al.**⁽¹⁶⁾ presented animal models-based and clinical evidences that support asymptomatic hyperuricemia as a causative risk factor in hypertension. They added that uric acid lowering drugs might be beneficial to prevent or delay early HTN among asymptomatic hyperuricemic patient, while not in long-established HTN. However, the current results found that HTN was a potential causative factor for eliciting gout symptoms in hyperuricemic patients. The prevalence of hyperuricemia and gout symptoms steadily raised among the blood pressure groups. This association was also significant after applying multivariate regression analysis to adjust for confounders or risk factors such as age, gender, BMI, and smoking. All the untreated hypertensive patients (100%) showed elevated UA levels and were significantly symptomatic suggesting that HTN might be a cause of hyperuricemia and flaring of gouty arthritis.

The finding of the untreated HTN group showed patients with UA level restricted to one category, more than 360 $\mu\text{mol/L}$, and all were symptomatic. The controlled HTN group showed variations in the UA levels (52.3% had UA levels $>360 \mu\text{mol/L}$, 39.5% had UA levels 157-360 $\mu\text{mol/L}$, and 8.2% had UA levels $<157 \mu\text{mol/L}$), and all the group's participants were asymptomatic for gout. This was a regular finding for those having lower UA levels as evidenced by previous study reporting that serum uric acid less than 360 prevent monosodium urate crystal deposition⁽¹⁷⁾, however the gout symptoms-free hyperuricemic patients were an odd finding and didn't meet the result of any prior studies. The results of both PB groups could be an indicator of the tendency of the hypertensive patients to have manifest hyperuricemia. Therefore, these findings could support

the authors' assumption that hypertension is a gout-associated comorbidity, maintained hyperuricemia, and is involved in the appearance of gouty symptoms. Although all participants included in the controlled HTN group had no gout symptoms, several previous studies recommend the use of UA-lowering drugs in asymptomatic hyperuricemia to avoid the expected pathological alterations caused by UA-induced inflammation and oxidative stress⁽¹⁸⁾.

Previous literature studies have concluded a correlation between NO production, oxidative stress, xanthine oxidase, hypertension, and hyperuricemia as an explanation for the HTN-induced manifest hyperuricemia. A previous study⁽¹⁹⁾ reported a reduced NO production in patients with essential hypertension patients. An experimental study, **Khosla et al.**⁽²⁰⁾ reported that hyperuricemic rats have a decrease in their serum NO, which was reversed by decreasing uric acid levels. Moreover, they found that soluble uric acid could impair NO release in cultured endothelial cells. In their later work, **Touyz et al.**⁽¹⁷⁾ reported an increase in xanthine oxidase, an increase in oxidative stress biomarkers, and a decrease in NO in experimental hypertension.

So, the uncontrolled BP can lead to hyperuricemia through different mechanisms; increased xanthine oxidase and uric acid production, through renal insufficiency mainly due to a decreased NO production, or directly by increased glomerular pressure and glomerulosclerosis. Added to this, the oxidative stress associated with hypertension could stimulate the deposition of monosodium urate crystals, and hence the appearance of symptoms.

The above-mentioned studies further supported the current finding of absent gout symptoms in treated hypertensive patients with controlled BP. In more confirmation, **Chalès**⁽²¹⁾ and **Chen et al.**⁽²²⁾ added that the treatment of gout flare by UA lowering therapies only are not optimal and just improves the quality of life, and the optimal management of cardiovascular and other comorbidities associated with hyperuricemia is a matter of urgency.

All patients of the uncontrolled HTN group were symptomatic for gout, the vast majority (91.4%) showed high UA ($> 360 \mu\text{mol/L}$); meanwhile the remaining 8.6% showed high normal UA levels (315 ± 1.5). Interestingly, all patients with controlled HTN (on regular HTN medications) were asymptomatic, although more than half of those patients (52.3%) showed high UA level more than 360 $\mu\text{mol/L}$. Also, the correlation study indicated a significant positive relationship with both the number and duration of gout joint flares. The more controlled blood pressure, the less frequent is the attacks/year and is the short duration of each, which further emphasizes the importance of BP in manifesting hyperuricemia.

CONCLUSION

The prevalence of gout symptoms was high in patients with uncontrolled blood pressure. The gout symptoms were strongly associated with hypertension among the Saudi patients and the prescription of blood pressure lowering therapies might be advantageous in the management strategy of gout symptoms. The current research shed light on the importance of follow up and proper control of blood pressure in hyperuricemic/gout patients as this approach might lead to a decrease or even an avoidance of the concomitant use of uric acid lowering drugs and their side effects. The study finding might be a basis to modify the current management strategy and the physicians' concept to prioritize the control of blood pressure.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

All authors have contributed equally to the preparation of the manuscript.

Strengths and limitations

The present study holds its strengths and limitations. Firstly, to the authors' knowledge, the current study was the first attempt to declare an association between the occurrence of gout symptoms in hyperuricemic patients and the improper control of blood pressure. However, some limitations should also be addressed. Firstly, the main limitation was its cross-sectional nature, which interfered with making a causal inference based on our results. Thus, the current results remained to be confirmed by prospective studies. Second, the medical records were not computerized, so much data were excluded due to missed and or unclear patients' information (which was reflected on the small sample size). However, the data collection was conducted manually by the investigation of the printed medical files, the selected participants were obtained from the KSMC, which is a big central core for electronic archiving of the serial numbers of the patient medical records that allowed easier filtration of the hypertensive hyperuricemic patients, which was not available in other Saudi cities' hospitals.

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Disclosure

The authors declare that they have no competing interests.

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