Research Article

Risk of Hypertension in Obese Gouty Patients: a Case-Control Study

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Abstract
Background: Gout is one of the most common rheumatic diseases and hypertension is one of the common comorbidities of gout. The combination of hypertension with metabolic abnormalities is of great importance. The development of gout is associated with obesity-induced metabolic abnormalities however a substantial number of non-obese patients also develop gout. **Objective:** to determine the association between hyperuricemia, obesity and hypertension. **Method:** A total of ٢٠٠ Saudi patients who underwent health examination at outpatient clinic of rheumatology in Hussain Al-Ali hospital, were selected and divided into obese and non-obese groups for determining the relationship between serum uric acid, obesity and hypertension. **Result:** systolic, diastolic blood pressure and BMI were significantly higher in cases than in controls. Obesity and hyperuricemia were associated with higher risk for hypertension, where the odds ratio for obese gouty patients was ٤.٣٦ (٩٥٪ CI: ١.٩٠ – ٩.٩٦, $p < ٠.٠٠١$) and ٢.٨٧ (٩٥٪ CI: ١.١٦ – ٧.١١, $p < ٠.٠١$) for non-obese gouty patients. Linear regression analysis showed that both blood pressure and serum uric acid were significantly ($p < ٠.٠٠١$) associated with BMI. The prevalence of hypertension was (٢٧.٥٪ vs ١٦.٢٥٪, $p < ٠.٠٠١$) in obese and non-obese groups in comparison to the control group respectively. **Conclusion:** This study supported the association of both obesity and hyperuricemia with hypertension. Showing that obese gouty patients have higher risk for developing hypertension than non-obese and both have higher risk than controls.
Keywords: hyperuricemia, obesity, hypertension and odds ratio.

Introduction
Gout is one of the most painful and common inflammatory arthritis[١]. Gouty arthritis is a common painful inflammatory arthritis with sudden onset, characterized by deposition of monosodium urate crystals in affected joints and surrounding tissue[٢]. The initial manifestation of gout is the acute arthritis however other manifestations such as subcutaneous tophi, chronic joint damage, and periarticular inflammation are common[٣]. Since gout results from deposition of urate crystals so urate-lowering drugs (ULD) that can prevent crystal formation and dissolve existing crystal deposits may play an important role in treatment of gout[٤]. Gout is also associated with comorbidities that may weaken prosperity and reduce the long life[٥]. Gout may be associated with many diseases such as nephrolithiasis[٦], cardio-vascular diseases[٧-٩] chronic renal impair-ment[١٠] hypothyroidism[١١], anemias[١٢] and metabolic syndrome[١٣] and to less extent cancer[١٤].

Current clinical guidelines and recommend-dations endorsed by the European League against Rheumatism[١٥], American College of Rheumatology[١٦] and British Society for Rheumatology/British Health Professionals in Rheumatology[١٧] agree on the impor-tance of comorbidity on gout management but only discuss diseases that are recognized to be pathophysiologically related to gout. In addition, ULD is recommended only for patients with high urate level or with comorbidities such as poor kidney function. There are many complicated patients with multiple comorbidities that are directly related to gout. The management decision in such cases is often difficult since recommend-dations and guidelines give no specified guidance in these scenarios[١٨].

World Health Organization (WHO) considers obesity as a worldwide epidemic and currently on increase. According to the WHO in ٢٠٠٥, approximately ١.٦ billion adults over the age of ١٥ were overweight. At least ٤٠٠million adults were considered obese and ≥٢٠million children under the age of ٥years were overweight. The estimation for (٢٠١٥) is approximately ٢.٣ billion overweight adults and over ٧٠٠ million obese ones[١٩]. Obesity may be implicated in different serious health problems such as hypertension, heart failure, diabetes mellitus, coronary disease, infertility, hyperlipidemia and increased prevalence of different kinds of cancer including colon, prostate, and breast cancer[٢٠]. Many researches tried to illustrate how obesity cause hypertension however the exact mechanism still unclear[٢١]. One of the explanations depends on implication of the activated sympathetic nervous system another one depends on the amount of visceral fat, the most likely one depends on sodium retention that can increase the renal reabsorption, and the renin-angiotensin system, are considered to have important functions in the pathogenesis of obesity-related hypertension[١٩].

One of the important risk factors for morbidity and mortality is hypertension[٢٢]. Hypertension especially if uncontrolled can lead to many health issues , including coronary artery disease, aneurysms, kidney disease or even peripheral artery disease[٩, ٢٣-٢٥]. Hypertension not only has an obvious economic impact represented in medical costs, but also decreases human productivity[٧]. According to the Global Burden of Disease ٢٠١٠, hypertension was the major risk factor for death in KSA[٢٦], it represents ٢٤٪ of total deaths from cardiovascular and ١.٨٧٪ from hypertensive urogenital and endocrine diseases[٨]. So, our objective was to determine the risk of hypertension in the gouty obese individuals and also association of hyperuricemia with obesity and hypertension.

Patients and method

Two hundred gouty male patients were selected from the outpatient clinic of rheumatology in Hussain Al-Ali hospital, KSA in the period from August ٢٠١٤ until July ٢٠١٥. Patients with diabetes, kidney diseases, dyslipidemia in addition to the autoimmune diseases were excluded. Besides the patients one hundred healthy controls were selected with matched age.

Systolic and diastolic BP was measured in all of the subjects. The diagnosis of hypertension was based on a systolic BP of ١٤٠ mmHg or higher and a diastolic BP of ٩٠ mmHg or higher. Patients who were on drugs for hypertension were considered hypertensive even if the measured diastolic or systolic blood pressure did not exceed ٨٩ or ١٣٩mmHg, respectively.

To assess obesity, height and weight were measured and body mass index (BMI) was calculated as the weight in kilograms (kg) divided by the square of the height in meters (m). According to the recent guidelines for obesity the value of BMI is now used to diagnose the stage of overweight or obesity. Considering BMI at ٢٥ -٢٩.٩ as overweight, while a BMI>٣٠ is considered as obesity[٢٧] Hyperuricemia was defined as serum uric acid level over ٧.٠ mg/dl. The patients were categorized according to the BMI, serum uric acid and blood pressure as obese, hyperuricemia or hypertensive patients. Gout was diagnosed according to ١٩٧٧ ACR criteria.

Statistical analysis

Baseline characteristics between controls and patients were compared with the Anova analysis followed by *t*-test between the groups. Odds ratio was calculated using the free program at http://vassarstats.net/odds٢x٢.html. We used graphpad prism to calculate the correlation and linear regression analysis.

Results

A total of ٢٠٠ gouty patients and ١٠٠ controls were included in this study. Baseline characteristics of the patients divided into two groups according to BMI are presented in table ١. Anova analysis showed a significant difference ($p < ٠.٠٠١$) between the three groups concerning the BMI, serum uric acid, systolic and diastolic BP but insignificant difference concerning

the age. Moreover, Anova analysis followed by *t*-test between the groups showed that there was no significant difference between the obese and non-obese group concerning the age and serum uric acid.

Table (١): Baseline characteristics of the subjects and controls

Variable	Control (n=١٠٠)	Obese (n=١٢٠)	Non-obese (n=٨٠)
Age (years)	٣٦.١٨ ± ٩.٠٩	٣٥.٢٩ ± ٩.٤٢	٣٦.٨٠ ± ١٠.١٤
Systolic BP(mmHg)	١٢١.٠٥ ± ١٠.٦٧	١٢٩.٢٠ ± ١٤.٨٥***	١٢٥.٣٧ ± ١٢.٨١
Diastolic BP(mmHg)	٧٧.٦٤ ± ٣.٩٩	٨١. ٥٨ ± ٨.٣٠***	٧٩.٣٨ ± ٧.٣٠
Height (m)	١.٧٣ ± ٠.٠٧	١.٧١ ± ٠.٠٦	١.٧٢ ± ٠.٠٧
Weight (kg)	٦٨.٠٩ ± ٧.٦١	٩٨.٥٦ ± ١٠.٨***	٦٨.٤٨ ± ٧.٣٨
BMI (kg/m^{٢})	٢٢.٧ ± ١.٧٦	٣٣.٥٠ ± ٢.٨٩***	٢٣.٠٨ ± ١.٣٨
Uric acid (mg/dl)	٤.٦٦ ± ٥٩	٩.٦٨ ± ١.٦٨***	٩.٣١ ± ١.٣٠***

Anova analysis followed by *t*-test were used to calculate the variance between the groups. Where * p<٠.٠٥ and *** p<٠.٠٠١

Risk of hypertension in the obese gouty patients as shown in table ٢, the odds ratio for obese patients was ٤.٣٦ (٩٥٪ CI: ١.٩٠ - ٩.٩٦, p < ٠.٠٠١) and for non-obese was ٢.٨٧ (٩٥٪ CI: ١.١٦ – ٧.١١, p < ٠.٠١). While the odds ratio for obese *vs* non-obese was ١.٥١ (٩٥٪ CI: ٠.٧٦ – ٢.٩٩, p = ٠.٢٢). Indicating that obese gouty patients had ٤.٣٦ higher chance of gaining hypertension than normal individuals while the non-obese gouty patients had ٢.٨٧ higher chance as com-pared to normal subjects. Although there is no statistical significant difference between the obese and non-obese gouty patients, the obese have ١.٥ higher chance of gaining hypertension than the non-obese.

Groups	Odds ratio	٩٥ CI	Chi-square
Obese	٤.٣٦	١.٩٠ – ٩.٩٦	P < ٠.٠٠١
Non-obese	٢.٨٧	١.١٦ – ٧.١١	P < ٠.٠١
Obese *vs* non-obese	١.٥١	٠.٧٦ – ٢.٩٩	٠.٢٢

Table (٢): Associated risk of hypertension in gouty patients

Both obese and non-obese gouty patients showed a significant (P < ٠.٠٠١) statistical risk of hypertension in comparison to the controls. Although there was no significant statistical difference between the obese and non-obese, the risk of hypertension was ١.٥١ times higher in the obese individuals than in the non-obese individuals. (Where ٩٥CI is a confidence interval).

After performing linear regression analysis as shown in figure-١, the BMI was significantly associated with systolic BP ($r^{٢}$ = ٠.١١٨, ٩٥٪ CI ٠.١٧٥ to ٠.٤٩٣, p < ٠.٠٠١) and diastolic BP ($r^{٢}$ = ٠.١٣٣, ٩٥٪ ٠.١٩٨ to ٠.٥١٠, p < ٠.٠٠١). On the other hand, uric acid was significantly associated with BMI ($r^{٢}$ = ٠.٤١٣, ٩٥٪ ٠.٥٢٤ to ٠.٧٣٧, p < ٠.٠٠١). However the association between BMI and age was insignificant. ($r^{٢}$ = ٠.٠٢٦, ٩٥٪ ٠.٠١٦ to ٠.٣٣٢, p < ٠.٠٧). The association between the serum uric acid and both systolic and diastolic BP was significant ($r^{٢}$ = ٠.١٥٢, ٩٥٪ ٠.٢٢٦ to ٠.٠.٥٣٢, p < ٠.٠٠١)

and (r^2 = ٠.٠٦٥, ٩٥٪ ٠.٠٧٩ to ٠.٤١٥, p < ٠.٠١) respectively. The association between systolic BP and both BMI and serum uric acid was stronger than the association between diastolic BP and both BMI and serum uric acid. As shown in figure-٢, the prevalence of hypertension was high in the obese and non-obese groups, (٢٧.٥%) and (١٦.٢٥٪) respectively as compared to control (٨٪) (p< ٠.٠٠١).

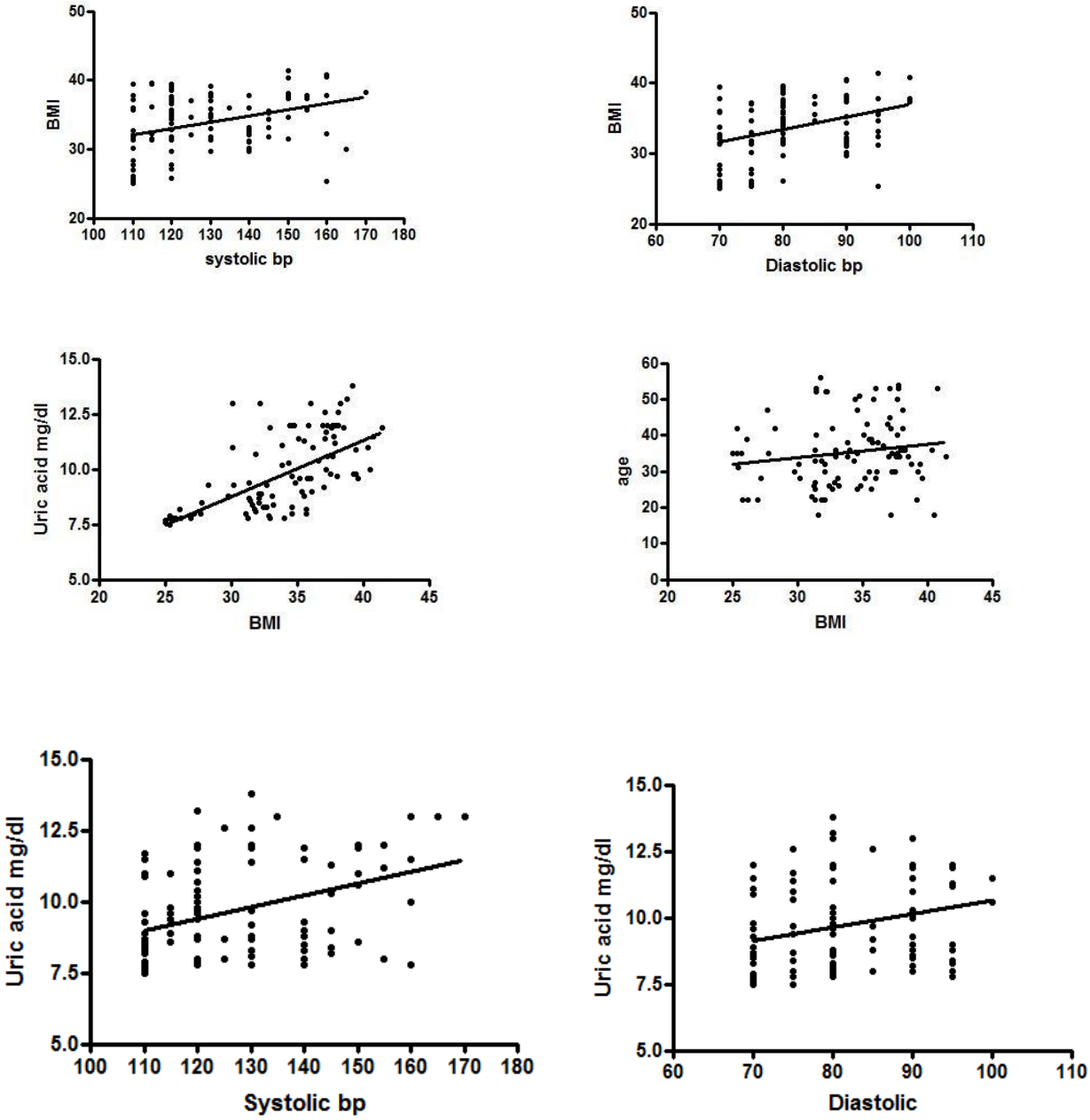


Figure (١): Associations between BMI, uric acid and blood pressure

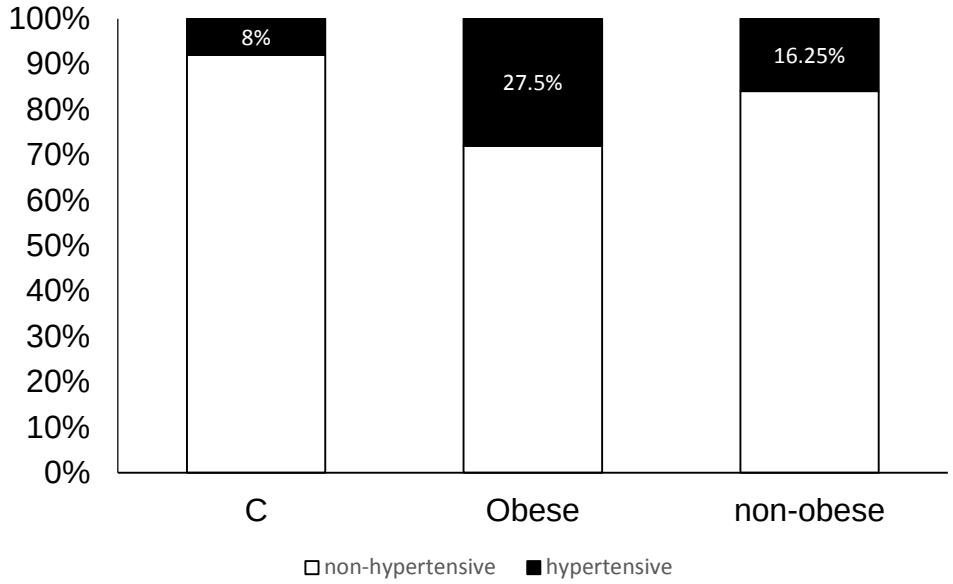
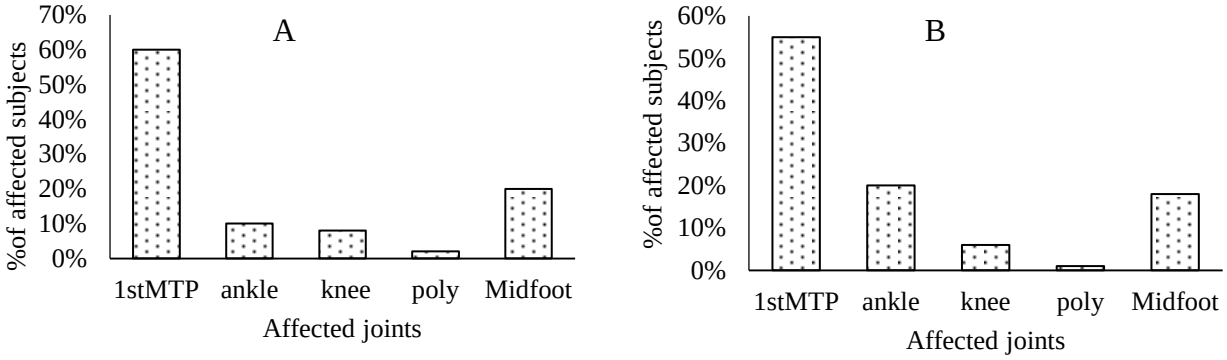


Figure (٢): Prevalence of hypertension in obese and non-obese gouty patients. A significant difference between obese and non-obese patients was seen among the total subjects who were included ($p < ٠.٠٠١$).



A) Affected joints in the obese patients **B) Affected joints in the non-obese patients.**

Figure (٣): Affected joints in the gouty patients:

Discussion

This study demonstrated the relationship between hyperuricemia, general obesity, gouty arthritis and the development of hypertension. As expected, there was a synergistic combined effect for obesity and hyperuricemia on hypertension development as compared with individual effects. Furthermore, the impact of obesity on hypertension development was highly significant, which is comparable to previous reports[١٩, ٢٧-٢٩]. Though there are a lot of reports on the effect of obesity on hypertension, the exact mechanism of how obesity causes hypertension is unclear. The most acceptable explanation is implication of adipose tissue and neuroendocrine mechanism behind the link between obesity and hypertension[٣٠]. Obesity has an effect on a reasonable number of hormones and the renin-angiotensin-aldosterone system is the most commonly affected. This system plays a main role in controlling the blood volume along with the sympathetic nervous system that is responsible for controlling the level of sodium and water retention. As

it reported obesity interferes with both of these mechanisms so it can be implicated in hypertension development[٢٨]. In addition to the above mentioned mechanisms, deposition of fats affects the kidney functions hence can alter the blood pressure.[١٩] Our current study has shown the contribution of metabolic factors in the development of hypertension. Since serum uric acid strongly correlated with BMI, it is possible that combination of both obesity and hyperuricemia triggers the development of hypertension.

In this study, we found a strong association between hyperuricemia and hypertension. The association of hyperuricemia and different diseases such as diabetes, cardiovascular diseases and kidney disease have been reported in several studies[٣١-٣٥]. Understanding the relation between a disease and the probable risk factor may be important in choosing the treatment strategy as the case of hyperuricemia and hypertension. Feig et al.,[٣٦] reported that uricosuric drugs can prevent hypertension development in individuals with hyperuricemia, this in accordance with the findings from animal models that illustrate the mechanism of hypertension development in the hyperuricemic animals. This mechanism consists of two phases; Uric acid induces vasoconstriction through the activation of renin-angiotensin system followed by cellular proliferation and arteriosclerosis due to uptake of uric acid by vascular smooth muscle cells. This case of early hypertension is uric acid dependent and sodium independent. On the other hand, the chronic hypertension is sodium dependent and uric acid independent[٣٤, ٣٧] also chronic hyperuricemia may induce microvascular renal disease which is responsible for development of hypertension[٣٤].
According to the results which obtained from experiments in rats, prolonged mild hyperuricemia causes irreversible salt-sensitive hypertension. If we generalized the animal results to humans, a two-staged development of hypertension is suggested; a uric acid-dependent, salt insensitive, and this is early stage and reversible, on the other hand, chronic hypertension is salt-sensitive and uric acid independent and it is irreversible hypertension[٣٨]. Mild hyperuricemia not only induces renal inflammation but also down regulates nitric oxide metabolism[٣٩], all of which are potentially important pathways leading to uric acid-mediated hypertension. In agreement with other studies[٢٩, ٣٩, ٤٠], our study demonstrated a strong association between hyperuricemia and hypertension in gouty patients and the risk of hypertension increases when hyperuricemia is associated with obesity.

Conclusion

This case control study supported the association of both obesity and hyperuricemia with hypertension. Showing that obese gouty patients have higher risk for developing hypertension than non-obese and both have higher risk than controls.

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