

## Original Research

# Urolithiasis in Primary Gout, Incidence of Clinically Presented and Asymptomatic Kidney Stones: Identification of Significant Risk Factors

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## ABSTRACT

**Background**

The aim of this study is to explore the prevalence of urolithiasis in patients with primary gout as well as its correlation with other associated risk factors.

**Methods**

The study was conducted on 102 patients with primary gout, they underwent ultrasonography examination and their general, clinical, and urinalysis data were recorded for further assessment and statistical analysis.

**Results**

There were 102 patients with primary gout included in our study, 69 (67.6%) males, mean age of patients was  $64.3 \pm 9.7$ . The overall prevalence of urolithiasis in our patients with primary gout is 37.3% and 15.7% have "silent" urolithiasis. Patients with urolithiasis (Group 1) are significantly older,  $68.9 \pm 7.4$ -years, had a long history of gout  $10.3 \pm 4.5$ -years, presence of tophi in 9 (23.6%) patients and more than 3 gouty arthritis attacks per year in 17(44.7%) patients. Also, patients in Group 1 have a significantly lower urine pH of  $5.2 \pm 0.4$  compared to patients without urolithiasis (Group 2) who have a urine pH of  $6.6 \pm 0.2$ . Results showed that obesity, diabetes, and hyperlipidemia are significantly more common in patients with urolithiasis (Group 1) while the presence of hypertension is not significantly different between groups. Correlation between urolithiasis and parameters related to disease (duration, tophi, and more than three attacks per year) and parameters related to urinalysis (pH and crystalluria) was tested and found statistically significant. Logistic regression analyses (univariate and multivariate) of tested parameters confirmed that obesity, diabetes mellitus, and hyperlipidemia are predictive factors for the presence of urolithiasis in patients with primary gout.

**Conclusion**

There is a high prevalence of urolithiasis in patients with primary gout including asymptomatic urolithiasis, associated with the age of patients, duration, and severity of gout, obesity, diabetes, and hyperlipidemia. Therefore, ultrasonographic screening as harmless and available should be recommended in order to prevent complications.

**Keywords**

Spontaneous; Bladder; Rupture; Atraumatic; Urine extravasation.

## INTRODUCTION

Gout is by far the most common arthritis in adults worldwide and its prevalence is rapidly growing. The prevalence of physician-diagnosed gout in the US has been reported as 3.9%, with male to female ratio of 3:1.<sup>1</sup>

Urolithiasis is very often associated with gout and

hyperuricemia, and numerous studies have been conducted regarding this connection. The association between gout and urolithiasis was investigated on a cohort of 51,529 male subjects and it was found that the prevalence of kidney stones was almost twice as high in respondents who had gout compared to those without this diagnosis (15% versus 8%). After adjustment for age and body mass index (BMI), gout was still significantly associated

with urolithiasis (OR 1.88; 95% CI 1.68-2.11). Multivariate analysis found that the relative risk of urolithiasis in people with gout was higher than in the healthy population (RR 2.12; 95% CI 1.22-3.68), and in contrast, urolithiasis was not associated with an increased risk of gout (RR 1.05; 95% CI 0.54-2.07) (124). Also, primary gout and urolithiasis are associated with metabolic syndrome elements like obesity, hyperlipidemia, and diabetes.<sup>2,3</sup>

The aim of the study is to find out the prevalence of urolithiasis, clinically presented and asymptomatic in our patients with primary gout, and to identify additional risk factors for this condition.

## MATERIAL AND METHODS

This research was conducted on 102 patients diagnosed with primary gout according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria. The attending rheumatologist filled in all necessary data to research protocol (general data, clinical findings, and laboratory results) and referred a patient to ultrasonography.

The following clinical parameters were assessed: age, gender, duration of disease (gout), the presence of tophi, average number of acute arthritis episodes per year, BMI, presence of diabetes mellitus, hypertension, and hyperlipidemia.

From urinalysis data, we followed urine pH and the presence of crystals in urine. Clinical presentation of urolithiasis was noted as positive if the patient reported that he has/had a kidney stone or episode of colic pain connected with kidney stone passage to urine.

Ultrasonography findings regarding the presence of urolithiasis, location, and size of the stone, as well as the presence of hydronephrosis were filled in the research protocol from the ultrasonography report. The ultrasonography examination was performed by the same urologist subspecialized in urology ultrasound examination using a curvilinear probe with a transmit frequency of 2.5-6.0 MHz in multiple anatomic planes.

For the statistical analysis was used statistical package for the social sciences (SPSS 22.0). Continuous variables were compared using Student's *t*-test and Mann-Whitney test as appropriate while categorical variables were compared using the chi-squared test and Fisher's exact test. Finally logistic regression analysis of tested parameters with regards to presence of urolithiasis and size of stones was performed. A two tailed *p* value of  $\leq 0.05$  was considered statistically significant.

## RESULTS

Our observed group of gout patient had in total 102 participants, all diagnosed with gout and assessed for presence of urolithiasis. The previously existing urolithiasis was reported by 22 (21.6%) of patients and ultrasonography screening confirmed urolithiasis within 38 (37.3%) of patients. It means that overall prevalence of urolithiasis in our patients with primary gout is 37.3% and that

15.7% has "silent" urolithiasis.

Furthermore, it is found that 15 (14.7%) of our gout patients suffer from bilateral urolithiasis, that 13(12.7%) has stones larger than 5 mm, and 7 (6.9%) has additional condition of hydronephrosis. All data regarding clinical and ultrasonographical finding of urolithiasis are presented in Table 1.

	<b>N=102</b>
Positive history of urolithiasis	22 (21.6%)
Ultrasonography finding of urolithiasis	38 (37.3%)
- Bilateral urolithiasis	15 (14.7%)
- Stones with a radius more than 5 mm	13 (12.7%)
- Hydronephrosis	7 (6.9%)
<i>Data presented as total number and percent (%)</i>	

The next step in our research was to evaluate differences between gout patients with presence of urolithiasis (Group 1) and without urolithiasis (Group 2).

First assessed parameter was age of patients and we found that patient in Group 1 with mean age 68.9 (SD $\pm$ 7.46) were statistically significant older than patients in Group 2 age 60.6 $\pm$ 9.9.

On the other hand, male gender was not connected with significantly more frequent finding of urolithiasis, Group 1 has 27 (71.1%) males and Group 2 42 (75.0%).

Characteristic of disease itself, like duration of gout and presents of tophi and more than three gouty arthritis attacks per year showed to be significantly different in Group 1 and Group 2. Patients in Group 1 had longer history of gout 10.3 $\pm$ 4.5-years, presence of tophi in 9 (23.6%) patients and more than 3 gouty arthritis attacks per year in 17 (44.7%) patients. At the same time patients at Group 2 had gout lasting 3.5 $\pm$ 2.2-years, presence of tophi in 6 (9.3%) patients and more than three episode of gouty arthritis attacks per year in 11 (17.1%) patients (Table 2).

Our next task was to compare groups regarding obesity and comorbidities (diabetes, hypertension and hyperlipidemia). Results showed that obesity, diabetes and hyperlipidemia are significantly more common in patient with urolithiasis (Group 1) while presence of hypertension is not significantly different between groups.

In Group 1 were 34 (89.4%) obese patients, 27 (71.0%) diabetics, 35 (92.1%) with hyperlipidaemia in comparison with 48 (75.0%) obese, 15 (23.4%) diabetics and 46 (71.8%) with hyperlipidemia in Group 2.

Further comparison was conducted in urinalysis results taking into consideration two specific parameters: pH of urine and presence of crystals in urine. Patients in Group 1 had pH of urine 5.2 $\pm$ 0.4, and positive crystalluria in 26 (68.4%) patients. On the

other side in Group 2 average urine pH was  $6.6 \pm 0.2$  and positive crystalluria in 4 (6.2%) patients. For both parameters difference between groups is statistically significant. Comparison between Group 1 and Group 2 as well as *p* values showing statistical significance of these differences are presented in Table 2.

**Table 2. Comparison between Patients with and without Urolithiasis**

Variable	Group 1	Group 2	<i>p</i> value
Age in years	68.9±7.4	60.6±9.9	<0.001
Male gender	27 (71.1%)	42 (75.0%)	0.573
Duration of gout in years	10.3±4.5	3.5±2.2	<0.001
Tophi	9 (23.6%)	6 (9.3%)	0.002
More than three episodes of arthritis episodes per year	17(44.7%)	11(17.1%)	0.011
Obesity (BMI over 25)	34 (89.4%)	48 (75.0%)	<0.001*
BMI 25-30	11(28.9%)	34(53.1%)	
BMI 30-35	15 (39.4%)	13(21.8%)	
BMI over 30	8 (21.0%)	0 (0%)	
Diabetes mellitus	27 (71.0%)	15 (23.4%)	<0.001
High blood pressure	35 (92.1%)	50 (78.1%)	0.068
Hyperlipidemia	35 (92.1%)	46 (71.8%)	0.015
Urine pH	5.2±0.4	6.6±0.2	<0.001
Crystalluria	26 (68.4%)	4 (6.2%)	<0.001

The data are presented as total number and percent (%), or mean value and standard deviation (±SD)  
\**p* value for the comparison among three obesity category subgroups

After finding significant difference between groups regarding parameters related to disease (duration, tophi and more than three attacks per year) and parameters related to urinalysis (pH and crystalluria) we tested significance of correlation between these parameters and presence of urolithiasis and found significant correlation in all tested values. Results are shown in Table 3.

**Table 3. Significance of Correlation between Urolithiasis and Parameters of Disease and Urinalysis**

Parameter	Pearson Correlation Coefficient	<i>p</i> value
Duration of gout	0.709	0.000
Tophi	0.310	0.02
More than 3 attacks/year	0.290	0.03
Urine pH	0.795	0.000
Crystalluria	0.660	0.000

\*Student's *t*-test

Finally, by using logistic regression analyze (univariate and multivariate) of tested parameters we confirmed that obesity, diabetes mellitus and hyperlipidemia are predictive factors for presence of urolithiasis in patients with primary gout. All data are presented in Table 4.

In order to explore possibilities of prediction of forming kidney stones with diameter more than 5mm, logistic regression analysis was performed regarding stone size. However, predictive value of this parameters for stone sizes in not significant. All dates

shown in Table 5.

**Table 4. Significance of Correlation between Urolithiasis and Parameters of Disease and Urinalysis**

Parameter	Univariate Logistic Regression Analysis		Multivariate Logistic Regression Analysis	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
BMI	3.337 (1.837-6.061)	<0.001	2.316 (1.198-4.4478)	0.013
DM	7.364 (2.991-18.128)	<0.001	4.097 (1.519-11.048)	0.005
HTA	3.267 (0.873-12.224)	0.079	-	-
HLP	4.565 (1.246-16.733)	0.022	3.618 (0.812-16.121)	0.092

**Table 5. Logistic Regression Analysis of Tested Parameters Regarding the Stone Size**

Parameter	Univariate Logistic Regression Analysis		Multivariate Logistic Regression Analysis	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
BMI	1.029 (0.478-2.215)	0.943	-	-
DM	0.613 (0.137-2.745)	0.613	-	-
HTA	>100	0.998	-	-
HLP	>100	0.998	-	-

## DISCUSSION

Different studies have reported a very different incidence of calculus in patients with gout, ranging from 10 to 40%.<sup>2</sup> The found prevalence of clinical-symptomatic urolithiasis in our sample is 21.6%, asymptomatic “silent” urolithiasis 15.7%, which means that the total frequency of urolithiasis in the observed group with primary gout is 37.3%.

The results obtained in this study show a high prevalence of calculus in this sample of patients, higher than that found in a somewhat older study conducted in the USA which confirmed urolithiasis in 13.9% of subjects with gout.<sup>3</sup> In this American study, only cases of manifest urolithiasis were considered, and the studied population was younger than the one followed in our sample.

More consistent results with our research were obtained by the authors who used computed tomography (CT) to determine nephrolithiasis, and the prevalence in their sample of 383 patients was 26.7% with 17.0% of “silent” calculi. And in this sample, which was more than three times larger than ours, the patients were also younger.<sup>4</sup>

Similar results to ours were presented in the work of Mexican authors who found that in the group of patients with gout, 39% had urolithiasis and 13% of the entire group received the first diagnosis of urolithiasis after an ultrasonographic examination.<sup>5</sup> A smaller number of studies were specifically concerned with determining the usefulness of ultrasonographic examination in the detection of urolithiasis in patients with gout. An earlier study

reports that ultrasound examination increases the possibility of diagnosing urolithiasis in patients with gout by 50%.

Our study found that ultrasonography enabled as many as 70% more diagnoses of urolithiasis. This obtained data is significantly higher, however, the probable explanation lies in the fact that our research was not population-based but was conducted on a sample of patients who had already consulted a rheumatologist and/or urologist. Earlier research conducted on a smaller number of patients with gout in the same study showed similar results with the appearance of urolithiasis in about 40% of subjects.<sup>6-8</sup>

Unfortunately, we were not able to provide computed tomography (CT) diagnostic for all our patients, which considered as first line diagnostic for urolithiasis, and consequently we didn't obtain data if stones were radiopaque or radiolucent to help as to differentiate uric acid stones from other types of stones, and that is drawback of our study.

Of the determined number of patients with urolithiasis in our study group, 65.7% had calculi less than 5 mm in size, and only 34.2% had calculi larger than 5 mm. This finding can be explained by the fact that the ultrasonographic examinations were performed in a period when the patients did not have symptoms of renal colic.

Of the total number of patients with urolithiasis diagnosed on ultrasound examination, 39.5% had bilateral urolithiasis, 42.1% had calculus on the left and 18.4% on the right. In the observed group of patients with primary gout, as many as 18.4% of respondents had signs of hydronephrosis during the ultrasound examination. These findings, which according to the findings of other authors are consistent with the findings of the clinical picture (absence of symptoms) of our subjects, point to the possibility of early diagnosis of urolithiasis, and give us time for preventive action before the formation of calculus of larger diameters and possible serious complications.<sup>9,10</sup>

In the observed group of 102 patients with gout average age is 64.3, in Group 1 68.6 and in Group 2 60.6. Statistical analysis has proven that the age is significantly higher in Group 1. Such findings are also consistent with earlier studies showing that urolithiasis is more common in older age.<sup>11,12</sup>

Regarding gender distribution in our sample of patients, in the whole group there were 67.6% men, in Group 1 71.1% men and in Group 2 65.6% men. These data indicate constant gender ratio in all groups, which is about 70% in favor of the male sex, with a slightly higher number in the group of patients with urolithiasis, but without a statistically significant difference. Although it is known that gout is a disease that is three times more common in men, and that urolithiasis as an entity is more common in the male population in our study there is no statistically significant difference according to gender in Group 1 and Group 2.

This result is most likely a consequence of the fact that only patients with gout were examined, therefore a difference according to gender was already made, which did not increase

statistically significantly by adding urolithiasis as another parameter.

In the observed sample of patients with gout, the average duration of the disease was 6.1-years. In Group 1-patients with urolithiasis, the duration of the disease is from 2 to 25-years with an average length of 10.3-years. In Group 2 of patients without urolithiasis, it is 1 to 15-years, and the average is 3.5-years. The above data clearly show that the longer the duration of gout, the higher the probability of urolithiasis.

Analytical statistics revealed a statistically highly significant difference between Group 1 and Group 2 in the duration of uric arthritis ( $p < 0.001$ ). Such results are a logical consequence of the already established fact that urolithiasis (especially urate) is more common with aging, but also the course of chronic gout itself, which leads to the formation of calculus due to urate deposition and later to interstitial urate nephropathy.<sup>13,14</sup>

Tophi are foci of deposited mono-sodium urates in the cartilage, tendon bursae and on the extensor sides of the joints, and on the auricles. They arise in chronic gout and as such represent an indicator of other comorbidities such as urolithiasis, but also predictors of a poorer quality of life.<sup>15</sup> Of the 102 patients we followed during our study, 14.7% had tophi, and even 2/3 were in the group with urolithiasis. In Group one, there were 23.6% of patients with tophi, and in Group 2 9.37% had tophi. Further data analysis revealed that there is a statistically significant difference in the presence of tophi between Group 1 and Group 2, in favor of Group 1.

The next observed parameter refers to the clinical presentation of gout and illustrates the course and severity of the disease and is the number of gouty arthritis attacks during the year. It was recorded how many patients have two or fewer attacks of arthritis per year and how many of them have three or more acute attacks of the disease during the year. It was found that 27.5% of patients in the entire observed group had three or more episodes of gouty arthritis, and that in Group 1 even 44.7% had three or more gouty arthritis attacks per year, while in Group 2, 17.1% of respondents fall into this category.

Analytical methods prove that this difference is statistically significant, that is, that patients with a greater number of gouty arthritis attacks per year are significantly more represented in Group 1, patients with urolithiasis. The number of gout attacks during the year indicates a probably long-term higher level of uric acid, which leads to an acute exacerbation of the underlying disease, but also to the appearance of complications, including urolithiasis and urate nephropathy.<sup>16,17</sup>

The presence of gout is, as already emphasized, an independent risk factor for the development of urolithiasis in men. The increased risk of urolithiasis is primarily related to urate calculus, but gout also increases the chance of calcium and phosphate calculi.

However, the most important risk factor for the formation of urate urolithiasis is long-term urine acidity, which induce urate

deposition. In our observed group, the mean value of urine pH is 6.1, which belongs to acidic urine, as can be expected in patients with gout.

In Group 1, the pH of urine ranges from 5 to 6 and the mean value is 5.2, while in Group 2 the pH is in the range from 5 to 8 and the mean value is 6.6, which is significantly less acidic urine, that is, a value closer to neutral. Through statistical processing, we found that there is a significant difference in the pH value between Group 1 and Group 2, that is, that the urine of patients with urolithiasis has a lower pH value.

Following the occurrence of crystalluria in 102 subjects, we found a positive finding in 29.4% of patients with gout. Group 1 had 68.4% of respondents with confirmed crystalluria and Group 2 only 6.2%. Of course, a statistically significant difference in the presence of crystalluria by observed groups was also proven. Our findings are analogous to the results obtained by American authors that uricosuria, acidic urine and low daily urine volume are crucial factors for the occurrence of urate lithiasis and that a change in diet, increased fluid intake and urine alkalinization could significantly reduce its frequency.<sup>18,19</sup>

Hyperuricemia is an integral part of the metabolic syndrome, along with hypertension, obesity, dyslipidaemia and insulin resistance. A Korean study showed a prevalence of metabolic syndrome (defined by National Cholesterol Education Program (NCEP) criteria<sup>20</sup> of 44% in patients with gout *versus* a prevalence of 5% in controls. In the US population, the prevalence of metabolic syndrome (defined by the same criteria) was 63% in patients with gout compared to a prevalence of 25% in controls without gout.<sup>21</sup> Men with gout are at increased risk for adverse cardiovascular events, and a diagnosis of gout is associated with a significantly increased with the risk of future development of type II diabetes, even after correction for the level of uric acid in the serum.<sup>22</sup> Research has shown that obesity and hypertension are independent risk factors for the development of gout.<sup>23</sup> On the other hand, urolithiasis also shows features of a systemic disorder,<sup>24</sup> especially urate urolithiasis, and it is stated that there is no basis for separating the entity of gout from idiopathic urate lithiasis with regarding of the presence or absence of arthritis.<sup>25</sup>

In the patients with gout that accompanied our research, 80.4% of the subjects were overweight (BMI over 25) and 7.8% were extremely obese (BMI over 35). In the USA, the relationship between BMI and gout was monitored in large national samples from 1988-1994 (16,521 subjects) and 2007-2010 (11,589 subjects), where a significant relationship between these two parameters was confirmed. In Group 1 there were 0.54% of patients with a BMI over 30, while in Group 2 there were 21.3%.

Through analytical processing, we obtained the data that obese patients are statistically significantly more represented in Group 1 with urolithiasis than in Group 2. Obesity has already been identified as an independent risk factor for the occurrence of urolithiasis, and in most cases, it is urate, which is explained by the low pH of urine in overweight patients weight.<sup>26</sup> An interesting result of our research is that even though excess body weight

accompanies gout, there is a difference in BMI between those with and without urolithiasis.

## CONCLUSION

The prevalence of urolithiasis in our patients with primary gout, overall is 37.3%, clinically presented urolithiasis has prevalence of 21.6% in comparison with 15.7% of prevalence of asymptomatic "silent" urolithiasis. The significant risk factors for urolithiasis in patients with primary gout are older age, the longer duration of gout, the more occurrence of nephrolithiasis, severity of illness (presence of tophi and more arthritis attacks during the year), lower pH of urine and presence of crystalluria, obesity, diabetes mellitus and hyperlipidaemia. The presence of last three signs of metabolic syndrome in our primary gout patients are significant predictors of urolithiasis, but not their size. Considering the presented findings, the obvious conclusion is that regular ultrasonographic screening for urolithiasis of patients with primary gout, especially those with risk factors, is very useful in prevention of serious complications.

## INSTITUTIONAL REVIEW BOARD STATEMENT

This study was observational, non-interventional, and did not require any Institutional Review Board (IRB) permissions to be conducted.

## CONSENT

All patients included in study were informed that their data would be used for research purposes.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

## REFERENCES

1. Singh JA, Gaffo A. Gout epidemiology and comorbidities. *Semin Arthritis Rheum.* 2020; 50(3S): S11-S16. doi: [10.1016/j.semarthrit.2020.04.008](https://doi.org/10.1016/j.semarthrit.2020.04.008)
2. Kramer HJ, Choi HK, Atkinson K, Stampfer M, Curhan GC. The association between gout and nephrolithiasis in men: The health professionals' Follow-Up Study. *Kidney Int.* 2003; 64(3): 1022-1026. doi: [10.1046/j.1523-1755.2003.t01-2-00171.x](https://doi.org/10.1046/j.1523-1755.2003.t01-2-00171.x)
3. Richette P, Bardin T. Gout. *Lancet.* 2010; 375 (9711): 318-328. doi: [10.1016/S0140-6736\(09\)60883-7](https://doi.org/10.1016/S0140-6736(09)60883-7)
4. Shimizu T, Hori H. The prevalence of nephrolithiasis in patients with primary gout: A cross-sectional study using helical computed tomography. *J Rheumatol.* 2009; 36(9): 1958-1962. doi: [10.3899/jrheum.081128](https://doi.org/10.3899/jrheum.081128)
5. Alvarez-Nemegyei J, Medina-Escobedo M, Villanueva-Jorge S, Vazquez-Mellado J. Prevalence and risk factors for urolithiasis in primary gout: Is a reappraisal needed? *J Rheumatol.* 2005; 32(11): 2189-2191.

6. Radosavljević Z, Milenković D, Radosavljević N. Učestalost urolitijaze kod pacijenata sa gihtom [In: Croatian]. *Acta Rheumatologica Belgradensia*. 2009; 39(1): 96.
7. Radosavljevic Z, Milenkovic D, Radosavljevic N. Frequency of urolithiasis in primary gout. *Eur Urol Suppl*. 2009; 8(8): 645. doi: [10.1016/S1569-9056\(09\)74995-4](https://doi.org/10.1016/S1569-9056(09)74995-4)
8. Radosavljevic Z, Savic S, Savic N, Radosavljevic N. Primary gout as a risk factor for urolithiasis. *Eur Urol Suppl*. 2011; 10(9): 589. doi: [10.1016/S1569-9056\(11\)61494-2](https://doi.org/10.1016/S1569-9056(11)61494-2)
9. Lallas CD, Liu XS, Chiura AN, Das AK, Bagley DH. Urolithiasis location and size and the association with microhematuria and stone-related symptoms. *J Endourol*. 2011; 25(12): 1909-1913. doi: [10.1089/end.2011.0265](https://doi.org/10.1089/end.2011.0265)
10. Ulsan S, Koc Z, Tokmak N. Accuracy of sonography for detecting renal stone: Comparison with CT. *J Clin Ultrasound*. 2007; 35(5): 256-261. doi: [10.1002/jcu.20347](https://doi.org/10.1002/jcu.20347)
11. Stansbridge EM, Griffin DG, Walker V. Who makes uric acid stones and why--observations from a renal stones clinic. *J Clin Pathol*. 2013; 66(5): 426-431. doi: [10.1136/jclinpath-2012-201373](https://doi.org/10.1136/jclinpath-2012-201373)
12. Walker V, Stansbridge EM, Griffin DG. Demography and biochemistry of 2800 patients from a renal stones clinic. *Ann Clin Biochem*. 2013; 50(Pt 2): 127-139. doi: [10.1258/acb.2012.012122](https://doi.org/10.1258/acb.2012.012122)
13. Kramer HM, Curhan G. The association between gout and nephrolithiasis: The National Health and Nutrition Examination Survey III, 1988-1994. *Am J Kidney Dis*. 2002; 40: 37-42. doi: [10.1053/ajkd.2002.33911](https://doi.org/10.1053/ajkd.2002.33911)
14. Grassi W, De Angelis R. Clinical features of gout. *Reumatismo*. 2012; 63(4): 238-245. doi: [10.4081/reumatismo.2011.238](https://doi.org/10.4081/reumatismo.2011.238)
15. Khanna PP, Nuki G, Bardin T, et al. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: Results from a cross-sectional survey. *Health Qual Life Outcomes*. 2012; 10: 117. doi: [10.1186/1477-7525-10-117](https://doi.org/10.1186/1477-7525-10-117)
16. Bakris GL, Doghramji PP, Keenan RT, Silber SH. CaseBook challenges: Managing gout, hyperuricemia and comorbidities -- dialogue with the experts. *Am J Med*. 2014; 127(1): S1. doi: [10.1016/j.amjmed.2013.11.001](https://doi.org/10.1016/j.amjmed.2013.11.001)
17. Kang DH, Nakagawa T. Uric acid and chronic renal disease: possible implication of hyperuricemia on progression of renal disease. *Semin Nephrol*. 2005; 25: 43-49. doi: [10.1016/j.semnephrol.2004.10.001](https://doi.org/10.1016/j.semnephrol.2004.10.001)
18. Sakhaee K. Epidemiology and clinical pathophysiology of uric acid kidney stones. *J Nephrol*. 2014; 27(3): 241-245. doi: [10.1007/s40620-013-0034-z](https://doi.org/10.1007/s40620-013-0034-z)
19. Bell DS. Beware the low urine pH--the major cause of the increased prevalence of nephrolithiasis in the patient with type 2 diabetes. *Diabetes Obes Metab*. 2012; 14(4): 299-303. doi: [10.1111/j.1463-1326.2011.01519.x](https://doi.org/10.1111/j.1463-1326.2011.01519.x)
20. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002; 106: 3143-3421.
21. Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: The Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2007; 57: 109-115. doi: [10.1002/art.22466](https://doi.org/10.1002/art.22466)
22. Choi HK, De Vera MA, Krishnan E. Gout and the risk of type 2 diabetes among men with a high cardiovascular risk profile. *Rheumatology (Oxford)*. 2008; 47: 1567-1570. doi: [10.1093/rheumatology/ken305](https://doi.org/10.1093/rheumatology/ken305)
23. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. *Arch Intern Med*. 2005; 165: 742-748. doi: [10.1001/archinte.165.7.742](https://doi.org/10.1001/archinte.165.7.742)
24. Sakhaee K. Nephrolithiasis as a systemic disorder. *Curr Opin Nephrol Hypertens*. 2008; 17(3): 304-309. doi: [10.1097/MNH.0b013e3282f8b34d](https://doi.org/10.1097/MNH.0b013e3282f8b34d)
25. Wiederkehr MR, Moe OW. Uric acid nephrolithiasis: A Systemic Metabolic disorder. *Clin Rev Bone Miner Metab*. 2011; 9(3-4): 207-217. doi: [10.1007/s12018-011-9106-6](https://doi.org/10.1007/s12018-011-9106-6)
26. Shavit L, Ferraro PM, Johri N, et al. Effect of being overweight on urinary metabolic risk factors for kidney stone formation. *Nephrol Dial Transplant*. 2015; 30(4): 607-613. doi: [10.1093/ndt/gfu350](https://doi.org/10.1093/ndt/gfu350)