

Nephrolithiasis among male patients with newly diagnosed gout

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ABSTRACT

Introduction: An elevated serum urate level is recognised as a cause of gouty arthritis and uric acid stone. The level of serum uric acid that accelerates kidney stone formation, however, has not yet been clarified. This study aimed to find out if a high serum urate level is associated with nephrolithiasis.

Methods: Patients were recruited from the rheumatology clinic of Taipei City Hospital (Renai and Zhongxing branches) in Taiwan from March 2015 to February 2016. A total of 120 Chinese male patients with newly diagnosed gout and serum urate concentration of >7 mg/dL and no history of kidney stones were divided into two groups according to their serum urate level: <10 mg/dL (group 1, n=80) and ≥10 mg/dL (group 2, n=40). The mean body mass index, blood urea nitrogen level, creatinine level, urinary pH, and kidney ultrasonography were compared between the two groups.

Results: There were no significant differences in blood urea nitrogen or creatinine level between the two groups. The urine pH in both groups was similar and not statistically significant. Kidney stone

formation was detected via ultrasonography in 6.3% (5/80) and 82.5% (33/40) of patients in groups 1 and 2, respectively (P<0.05).

Conclusion: A serum urate level of ≥10 mg/dL may precipitate nephrolithiasis. Further studies are warranted to substantiate the relationship between serum urate level and kidney stone formation.

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New knowledge added by this study

- Hyperuricaemia is a risk factor for renal stone formation, which is associated with a substantially higher prevalence of nephrolithiasis on ultrasonography.

Implications for clinical practice or policy

- Patients with gouty arthritis and serum urate level of ≥10 mg/dL should be advised to have renal ultrasonography.

Introduction

Over the past century, kidney stones have become increasingly prevalent, particularly in more developed countries. The incidence of urolithiasis in a given population is dependent on the geographic area, racial distribution, socio-economic status, and dietary habits.¹ In general, patients with a history of gout are at greater risk of forming uric acid stones, as are patients with obesity, diabetes, or complete metabolic syndrome.² Moreover, elevated serum urate levels are known to lead to gouty arthritis, tophi formation, and uric acid kidney stones.³ The incidence of uric acid stones varies between countries and accounts for 5% to 40% of all urinary calculi.⁴ Certain risk factors may be involved in the pathogenesis of uric acid nephrolithiasis, including low urinary volume and persistently low urinary pH.⁵

Calcium oxalate stones may form in some patients with gouty diathesis due to increased urinary excretion of calcium and reduced excretion of citrate. In addition, relative hypercalciuria in gouty diathesis with calcium oxalate stones may be due to intestinal hyperabsorption of calcium.⁶ Most urinary uric acid calculi are not pure in composition and complex urates, sodium, potassium, and calcium have been found together in various proportions.⁷ An analysis of stones in gout patients in Japan showed that the incidence of common calcium salt stones was over 60%, while that of uric acid stones was only 30%.⁸ This implies that the disruption of uric acid metabolism promotes not only uric acid stones, but also calcium salt stones. Therefore, a high serum urate level might be associated with nephrolithiasis and this provided the rationale for this study.

Methods

Overall, 120 male gouty arthritis patients with newly diagnosed gout and serum urate concentration of >7 mg/dL, and without previous kidney stone disease were allocated to one of the two groups according to their serum uric acid level: <10 mg/dL (group 1, n=80) and ≥10 mg/dL (group 2, n=40). Patients were recruited from the rheumatology clinic of Taipei City Hospital (Renai and Zhongxing branches), a tertiary community hospital in Taiwan, from March 2015 to February 2016. They had been newly diagnosed with gout but had no clinical suggestions of renal stone disease. The exclusion criteria included previously treated gouty arthritis and current prescription of urate reabsorption inhibitors. The patient's age, duration of gout arthritis, presence of tophi, body mass index (BMI), blood urea nitrogen (BUN), creatinine, urinary pH, and kidney ultrasonography were all measured and analysed. This study has been approved by the hospital's Institutional Review Board with informed consent waived.

Results for continuous variables were given as means ± standard deviations. Student's *t* test was used to compare the physical characteristics that were continuous in nature among the different subject groups and the Chi squared test was used to compare the difference in the stone detection rate between the two groups. A *P* value of <0.05 was regarded as statistically significant for two-sided tests. The Statistical Package for the Social Sciences (Windows version 12.0; SPSS Inc, Chicago [IL], US) was used for all statistical analyses.

Results

The mean age of the two study groups was similar (40 years). Family history of gout was present in 67.5% and 90% of groups 1 and 2, respectively. The time elapsed since onset of gout was less than 4 years in both groups. Tophaceous gout was found in 8.8% in group 1 and 10.0% in group 2. The prevalence of

初診痛風的男性患者的腎結石

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引言：血清尿酸水平偏高是痛風性關節炎和尿酸石的已知原因。血清尿酸水平上升可加速腎結石形成，惟兩者關係仍有待驗證。本研究旨在找出高血清尿酸水平與腎結石形成是否有關。

方法：研究對象為2015年3月至2016年2月期間到台灣臺北市立聯合醫院（仁愛院區和中興院區）風濕病門診的病人。共有120名初診痛風的男性華籍患者，無腎結石病史，血清尿酸水平均高於7 mg/dL。按血清尿酸水平把病人分為兩組：甲組的血清尿酸水平少於10 mg/dL（80人），乙組則有10 mg/dL或以上（40人）。比較兩組病人的平均身體質量指數、血尿素氮水平、肌酐水平、尿pH值和腎臟超聲檢查結果。

結果：兩組之間的血尿素氮水平和肌酐水平無顯著差異，尿pH值相若且未達統計顯著水平。通過超聲檢測發現甲組和乙組分別有6.3%（5/80）和82.5%（33/40）的病人有腎結石（*P*<0.05）。

結論：10 mg/dL或以上的血清尿酸水平可能誘發腎結石形成，但須進一步研究來證實血清尿酸水平與腎結石形成的關係。

patients with a BMI of ≥30 kg/m² was not statistically significant between the two groups. Only 6% of group 2 patients with kidney stones had a BMI of >95th percentile. In most cases, urinary pH was less than 5.5 in both groups and there were no abnormal changes to BUN or creatinine levels. Interestingly, the prevalence of kidney stones detected by ultrasonography was 6.3% in group 1 and 82.5% in group 2 (*P*<0.05). The sensitivity and specificity of high serum urate level (>10 mg/dL) in predicting kidney stones was 87% and 91%, respectively (Table).

Discussion

Gout is a common metabolic disorder characterised by chronic hyperuricaemia, and serum urate level of >6.8 mg/dL that exceeds the physiological threshold

TABLE. Risk factors of male gout patients with and without nephrolithiasis*

Risk factor	Group 1 (n=80), serum urate level <10 mg/dL	Group 2 (n=40), serum urate level ≥10 mg/dL	P value
Age (years)	40 ± 5	40 ± 7	0.061
Time elapsed since onset of gout (years)	<4	<4	0.312
Tophaceous gout	7 (8.8)	4 (10.0)	0.112
BMI (≥30 kg/m ²)	6	4	0.081
BUN (10-20 mg/dL)	13.41 ± 2.68	13.31 ± 2.52	0.754
Creatinine (0.6-1.2 mg/dL)	1.13 ± 0.24	1.32 ± 1.11	0.175
Urinary pH	5.48 ± 0.12	5.39 ± 0.14	0.072
Ultrasonography	5 (6.3)	33 (82.5)	<0.05

Abbreviations: BMI = body mass index; BUN = blood urea nitrogen

* Data are shown as mean ± standard deviation or No. (%) of patients, unless otherwise stated

of saturation. Urolithiasis is one of the well-known complications of gout. We hypothesise that serum urate level can be used as a predictive marker for urolithiasis. Uric acid, a weak organic acid, has very low pH-dependent solubility in aqueous solution. Approximately 70% of urate elimination occurs in urine, and the kidney plays a dominant role in determining plasma level.⁹ A serum urate level of >7 mg/dL is recognised as leading to gouty arthritis and uric acid stone formation. Moreover, recent epidemiological studies have identified serum urate elevation as an independent risk factor for chronic kidney disease, cardiovascular disease, and hypertension.³ Impaired renal uric acid excretion is the major mechanism of hyperuricaemia in patients with primary gout.¹⁰ The molecular mechanisms of renal urate transport are still incompletely understood. Urate transporter 1 is an organic anion transporter with highly specific urate transport activity, exchanging this anion with others including most of the endogenous organic anions and drug anions that are known to affect renal uric acid transport.^{10,11}

Uric acid stones account for 10% of all kidney stones and are the second most common cause of urinary stones after calcium oxalate and calcium phosphate. The most important risk factor for uric acid crystallisation and stone formation is a low urine pH (<5.5) rather than an increased urinary uric acid excretion.¹² The proportion of uric acid stones varies between countries and accounts for 5% to 40% of all urinary calculi.⁴ Uric acid homeostasis is determined by the balance between its production, intestinal secretion, and renal excretion. The kidney is an important regulator of circulating uric acid levels by reabsorbing about 90% of filtered urate and being responsible for 60% to 70% of total body uric acid factor underpinning hyperuricaemia and gout.¹³ Pure uric acid stones are radiolucent but well visualised on renal ultrasound or non-contrast helical computed tomographic scanning; the latter is especially good for detection of stones which are <5 mm in size.¹⁴ Nonetheless the reason why most patients with gout present with acidic urine, even though only 20% have uric acid stones, remains unclear. In a US study, the prevalence of kidney stone disease was almost two-fold higher in men with a history of gout than in those without (15% vs 8%).¹⁵ Higher adiposity and weight gain are strong risk factors for gout in men, while weight loss is protective.¹⁵ An analysis by Shimizu⁸ of stones in gout patients revealed that the proportion of common calcium salt stones was over 60%, while that of uric acid stones was only about 30%. Overweight/obesity and older age associated with low urine pH were the principal characteristics of 'pure' uric acid stone formers. Impaired urate excretion associated with increased serum uric acid is also another characteristic of uric acid stone

formers and resembles patients with primary gout. Patients with pure calcium oxalate stones were younger; they had a low proportion of obese subjects and higher urinary calcium.¹⁶

Conventionally, BMI was stratified as normal (<25 kg/m²), overweight (25-29.9 kg/m²), or obese (≥30 kg/m²). In males, the proportion of uric acid stones gradually increased with BMI, from 7.1% in normal BMI to 28.7% in obese subjects.¹⁷ The same was true in females, with the proportion of uric acid stones rising from 6.1% in normal BMI to 17.1% in obese subjects.¹⁷ Studies found that BMI is associated with an increased risk of kidney stone disease, but with a BMI of >30 kg/m², further increases do not appear to significantly increase the risk of stone disease.^{17,18} An independent association between kidney stone disease and gout strongly suggests that they share common underlying pathophysiological mechanisms.¹⁹

Three major conditions control the potential for uric acid stone formation: the quantity of uric acid, the volume of urine as it affects the urinary concentration of uric acid, and the urinary pH.²⁰ Two major abnormalities have been suggested to explain overly acidic urine: increased net acid excretion and impaired buffering caused by defective urinary ammonium excretion, with the combination resulting in abnormally acidic urine.²¹ Urinary alkalinisation, which involves maintaining a continuously high urinary pH (pH 6-6.5), is considered by some or many to be the treatment of choice for uric acid stone dissolution and prevention.²⁰ In general, gout is caused by the deposition of monosodium urate crystals in tissue that provokes a local inflammatory reaction. The formation of monosodium urate crystals is facilitated by hyperuricaemia. In a study by Sakhaee and Maalouf,²¹ being overweight and of older age were associated with low urine pH and one of the principal characteristics of pure uric acid stone formation. Impaired urate excretion associated with increased serum uric acid was another characteristic of uric acid stone formation that resembles patients with primary gout.

The limitations of this current study included the lack of measurement of uric acid concentration of urine in the participants, no further computed tomographic scanning for kidney stones, no analysis of stone composition, and limited representativeness of the study subjects. For example, there were only 10 obese patients (BMI ≥30 kg/m²) in the analysis. In this study, hyperuricaemia was a risk factor for kidney stone formation. Patients with serum urate level of >10 mg/dL should undergo ultrasound examination to look for any nephrolithiasis.

Declaration

All authors have disclosed no conflicts of interest.

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