A comparison of the metabolic profiles of diabetic and non-diabetic uric acid stone formers

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Abstract

Introduction: The aim of this study was to compare the metabolic profiles of diabetic and non-diabetic patients with uric acid stones to understand whether preventive strategies should be tailored to reflect different causative factors.

Methods: The results of the metabolic evaluation of patients with uric acid stones identified prospectively from the Metabolic Stone Clinic at St. Joseph's Hospital, London, Canada were reviewed. Information included patients' clinical histories, 24 hour urine collections, blood chemistry and stone analysis.

Results: Complete data were obtained from 68 patients with uric acid stones. Twenty-two patients had diabetes. There were no statistically significant differences in mean age, body mass index, or history of gout. Among diabetics, pure uric acid stones were identified in 14 patients (63%) and mixed uric acid in 8 (36%). Pure uric acid stones were more common in the diabetic cohort (63% vs. 46%, $p = 0.16$). Urine pH, serum and urine uric acid levels and 24-hour urine volumes were similar in both groups. The diabetic group had an increased average oxalate excretion (424 µmol/d vs. 324 µmol/d, $p = 0.003$).

Conclusion: The exact etiological basis for the higher oxalate excretion in diabetic uric acid stone formers is unclear. Whether this is a metabolic feature of diabetes, due to dietary indiscretion or the iatrogenic consequence of dietary advice requires further investigation.

Introduction

Uric acid stones account for about 7% of all human kidney stones and may be the result of congenital, acquired or idiopathic conditions.[1] An associated high rate of recurrence mandates concentrated efforts at identifying modifiable risk factors and developing preventive strategies.

The role of urine pH appears to be the most important factor influencing uric acid solubility and stone formation with supersaturation noted at a pH less than 6.[1] Various clinical conditions promote acidic urine, including chronic diarrhea, excessive purine intake and gouty diathesis (idiopathic low urine pH). It has been observed that non-insulin diabetics have a higher prevalence of uric acid stones, with low urine pH implicated in the pathogenesis.[2] There are some possible metabolic factors that may be responsible for this association.

Insulin resistance is the main characteristic of type II diabetes and may be associated with defects in renal ammonium production and an increase in urinary excretion of calcium.[3-5] In large epidemiological studies, body mass index (BMI) has been shown to be predictive of a higher risk of urolithiasis, although the magnitude of this effect appears to stabilize once the BMI exceeds 30.[6]

With the knowledge that uric acid stones can form due to various mechanisms in diabetic patients, we compare the metabolic profiles of diabetic and non-diabetic uric acid stone formers to elucidate differences which may represent new targets for preventive therapy.

Methods

From January 2002 to December 2010, all clinical data on patients who were managed at the Metabolic Stone Clinic at St. Joseph's Hospital in London, Ontario, Canada were prospectively entered into a database. Evaluation included a thorough clinical history, 24-hour urine collection, blood chemistry, urinalysis and stone analysis. The results were retrospectively analyzed after Research Ethics Board approval from Western University. We analyzed the records of 538 patients, 68 of whom had uric acid stones of pure or mixed composition (51 males, 17 females). Of these patients, 22 were non-insulin diabetics (17 males, 5 females). Standard urinary parameters were evaluated, including sodium, calcium, citrate, creatinine, uric acid, oxalate, potassium, phosphorous, cystine, pH and urine volume. Blood chemistry included sodium, potassium, chloride, bicarbonate, urea, creatinine, calcium, phosphate, uric acid, parathyroid hormone and vitamin D. All urine and blood testing was

performed with patients on their regular diet. Data from a subgroup of these patients known to have uric acid stones were extracted and statistical analysis was performed using GraphPad Prism v.4 software (GraphPad Software Inc., La Jolla, CA). Non-categorical variables were evaluated with unpaired *t*-tests, while categorical variables were compared with Fisher exact testing. Patients were categorized as having diabetes mellitus if they had type I or type II diabetes listed on their medical records or if they were on hypoglycemic medication, either oral hypoglycemics and/or insulin. Stone analysis was performed using infrared spectroscopy.

Results

There were no statistically significant differences with respect to gender, age, BMI, history of gout, spontaneously passed stones, or in the number of patients treated with ureteroscopy, percutaneous nephrolithotripsy (PCNL) or extracorporeal shockwave lithotripsy (SWL) (Table 1). None of the patients in this cohort had undergone gastric bypass surgery. Significantly more diabetics than non-diabetics were hypertensive (64% and 30%, $p = 0.02$).

Although both groups had acidic urine, differences in pH were not statistically significant. Stone analysis showed that in the diabetic group, pure uric acid stones were identified in 14 patients (63%), while mixed uric acid stones containing calcium oxalate were seen in 8 (36%). In the non-diabetic group, 21 patients had pure uric acid stones (46%) and 25 had mixed uric acid (calcium oxalate and phosphate) stones (54%). Pure uric acid stones were more common in the diabetic cohort than among non-diabetics (63% vs. 46%, $p = 0.16$), although this did not reach statistical significance. The diabetic group had a statistically significant increase in their average oxalate excretion and a significantly higher percentage of patients had hyperoxaluria and hypernatriuria. A greater proportion of non-diabetics had hyperchloremia, as well as higher serum sodium and a tendency towards lower urinary citrate levels (Table 2).

Table 1. Demographic and stone-related factors

	Diabetics	Non-diabetics
Demographics		
Male:Female	17:5	34:12
Average age [years] ± SD (range)	58 ± 12.33 (31–77)	54 ± 12 (30–76)
Average BMI ± SD (range)	35 ± 6 (23–47)	33 ± 7 (21–58)
History of gout	14%	12%
Stone history		
Spontaneously passed stones	71%	60%
Ureteroscopy	38%	29%
PCNL	33%	40%
SWL	33%	55%

SD: standard deviation; BMI: body mass index; PCNL: percutaneous nephrolithotripsy; SWL: shockwave lithotripsy.

Discussion

In the past 15 years, the number of cases of obesity, metabolic syndrome and diabetes mellitus has increased exponentially concurrent with an increase in the prevalence of urolithiasis. The association between the components of the metabolic syndrome and urolithiasis has been described previously by several groups.[3,7,8] The risk of kidney stones increases proportionally to the number of metabolic syndrome traits, such as glucose intolerance, obesity, low high-density lipoprotein (HDL) cholesterol, high triglycerides and hypertension.[9] In a large cohort of patients with a history of kidney stones, Maalouf and colleagues demonstrated an inverse relationship between body weight and urine pH.[10] A 3-fold increase in stone incidence and higher recurrence rates have been identified among diabetics and a history of diabetes increases the baseline risk of developing kidney stones by 38% in younger women, 67% in older women and 31% in men.[11] Daudon and colleagues found that uric acid stones were more common in diabetics. They also found an increased proportion of diabetes among uric acid stone formers than in calcium stone formers.[12] Type II diabetes was also identified as the strongest factor independently associated with the formation of uric acid stones.

Rather than occurring due to a single pathophysiological mechanism, uric acid calculi in the context of diabetes is likely to be multifactorial. Insulin resistance, which is seen in association with both diabetes and the metabolic syndrome, leads to defective ammoniagenesis, which results in low urine ammonium and pH.[3] This may manifest as uric acid precipitation, pure uric acid formation and mixed uric acid/calcium oxalate stones.

Various clinical conditions may predispose to uric acid stone formation. The physiochemical mechanisms are varied. The three most important metabolic factors influencing uric acid formation are urine pH <5.5, low urine volume and hyperuricosuria.[1] The exact role for crystal-crystal interactions of different structures, also known as epitaxy, continues to be evaluated. It is well-known that hyperuricosuria leads to elevated levels of monosodium urate which promotes calcium oxalate stones. Whether the observation of increased urinary oxalate is associated with an increase in calcium oxalate stone formation remains to be seen. Although hyperoxaluria was more common in our diabetic patients, pure uric acid stones were more frequent than the mixed uric acid/calcium oxalate stones than one might have predicted given the finding of hyperoxaluria.

Although diet has a well-recognized effect on urinary oxalate excretion, Taylor and Curhan highlighted that multiple mechanisms likely contribute in the context of diabetes.[13] This work demonstrated consistently higher urinary oxalate levels in diabetic patients, a finding that was durable despite controlling for both dietary oxalate and calcium.[13] Although the pathophysiology of this relationship has not been fully

Table 2. Metabolic parameters

	Diabetics N = 22	Non-diabetics N = 46	*p* value
Urinalysis	**Mean ± SD (range)**	**Mean ± SD (range)**	
24-hour volume (mL)	1820 ± 683 (398–3315)	1806 ± 746 (500–3771)	0.92
pH	5.5 ± 0.5 (5.0–6.5)	5.4 ± 0.4 (5.0–6.5)	0.66
Oxalate excretion (µmol/d)	424 ± 197 (83–887)	324 ± 153 (41–823)	0.003
Urine uric acid (mmol/d)	3.6 ± 2 (0.5–11)	3.6 ± 2 (0.8–6.5)	0.99
Urine citrate (mmol/d)	2.9 ± 2.4 (0.2-10.8)	2.5 ± 2.5 (0.1-12)	0.35
Blood chemistry	**Mean ± SD (range)**	**Mean ± SD (range)**	
Sodium (mmol/L)	138 ± 2 (134–144)	139 ± 2 (132–146)	0.16
Uric acid (µmol/d)	411 ± 121 (236–737)	414 ± 101 (227–661)	0.9
Percentage of patients			
Hyperoxaluric	54	24	0.03
Hypernatriuric	52	29	0.04
Hyperchloremic	10	50	0.03

SD: standard deviation.

delineated, it has been proposed that increased BMI and diabetes leads to changes in the metabolism of oxalate or an increase in endogenous oxalate production.[14] Hyperoxaluria has also been identified in hypertensive non-obese stone formers, although there is no indication whether any of the patients in the series were also diabetic.[15] Whether the hyperoxaluria noted in diabetics is exacerbated by dietary modifications implemented to manage the diabetes warrants further evaluation.

A number of contemporary series have reviewed the surgical outcomes for patients with diabetes.[16-18] In a series of 183 diabetic patients who underwent percutaneous nephrolithotomy, Duvdevani and colleagues[16] found that uric acid was the most common stone composition and that these patients had a longer hospital stay than non-diabetics. Surgical time, complications and stone-free rates were not significantly different from those observed in the non-diabetic group. Although surgical results are excellent, the metabolic derangements and the risk of ongoing stone-related events for uric acid formers and diabetics require attention for effective prevention. A thorough metabolic evaluation coupled with expert nutritional advice and tailored medical therapy remain essential components of a successful treatment regimen.

Conclusion

Our results show that diabetic uric acid stone formers had significantly higher levels of urinary oxalate compared with non-diabetic uric acid stone formers. Hypertension is also more common in this group. To our knowledge, there are no previous reports of hyperoxaluria in diabetic uric acid stone formers. The exact etiological basis of this observation and the clinical implications require further evaluation to tailor appropriate preventative strategies.

Competing interests: None declared.

This paper has been peer-reviewed.

References

1. Pearle MS, Lotan Y. Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, et al, eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA, Saunders Elsevier; 2007.
2. Pak CY, Sakhaee K, Moe O, et al. Biochemical profile of stone-forming patients with diabetes mellitus. *Urology* 2003;61:523-7. http://dx.doi.org/10.1016/S0090-4295(02)02421-4
3. Abate N, Chandalia M, Cabo-Chan AV Jr, et al. The metabolic syndrome and uric acid nephrolithiasis: Novel features of renal manifestation of insulin resistance. *Kidney Int* 2004;65:386-92. http://dx.doi.org/10.1111/j.1523-1755.2004.00386.x
4. Kerstetter J, Caballero B, O'Brien K, et al. Mineral homeostasis in obesity: effects of euglycemic hyperinsulinemia. *Metabolism* 1991;40:707-13. http://dx.doi.org/10.1016/0026-0495(91)90088-E
5. Nowicki M, Kokot F, Surdacki A. The influence of hyperinsulinaemia on calcium- phosphate metabolism in renal failure. *Nephrol Dial Transplant* 1998;13:2566-71. http://dx.doi.org/10.1093/ndt/13.10.2566
6. Semins MJ, Shore AD, Makary MA, et al. The association of increasing body mass index and kidney stone disease. *J Urol* 2010;183:571-5. http://dx.doi.org/10.1016/j.juro.2009.09.085
7. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *JAMA* 2005;293:455-62. http://dx.doi.org/10.1001/jama.293.4.455
8. Curhan GC, Willett WC, Rimm EB, et al. Body size and risk of kidney stones. *J Am Soc Nephrol* 1998;9:1645-52.
9. West B, Luke A, Durazo-Arvizu RA, et al. Metabolic syndrome and self-reported history of kidney stones: The National Health and Nutrition Examination Survey (NHANES III) 1988-1994. *Am J Kidney Dis* 2008;51:741-7. http://dx.doi.org/10.1053/j.ajkd.2007.12.030
10. Maalouf NM, Sakhaee K, Parks JH, et al. Association of urinary pH with body weight in nephrolithiasis. *Kidney Int* 2004;65:1422-5. http://dx.doi.org/10.1111/j.1523-1755.2004.00522.x
11. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int* 2005;68:1230-35. http://dx.doi.org/10.1111/j.1523-1755.2005.00516.x
12. Daudon M, Traxer O, Conort P, et al. Type 2 diabetes increases the risk for uric acid stones. *J Am Soc Nephrol* 2006;17:2026-33. http://dx.doi.org/10.1681/ASN.2006030262
13. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. *Clin J Am Soc Nephrol* 2008;3:1453-60. http://dx.doi.org/10.2215/CJN.01410308
14. Eisner BH, Porten SP, Bechis SK, et al. Diabetic kidney stone formers excrete more oxalate and have lower urine pH than nondiabetic stone formers. *J Urol* 2010;183:2244-48. http://dx.doi.org/10.1016/j.juro.2010.02.007
15. Kim YJ, Park MS, Kim WT, et al. Hypertension influences recurrent stone formation in nonobese stone formers. *Urology* 2011;77:1059-63. http://dx.doi.org/10.1016/j.urology.2010.07.492
16. Duvdevani M, Nott L, Ray AA, et al. Percutaneous nephrolithotripsy in patients with diabetes mellitus. *J Endourol* 2009;23:21-6. http://dx.doi.org/10.1089/end.2008.0282
17. Tefekli A, Kurtoglu H, Tepeler K, et al. Does the metabolic syndrome or its components affect the outcome of percutaneous nephrolithotomy? *J Endourol* 2008;22:35-40. http://dx.doi.org/10.1089/end.2007.0034
18. Turna B, Nazli O, Demiryoguran S, et al. Percutaneous nephrolithotomy: variables that influence hemorrhage. *Urology* 2007;69:603-7. http://dx.doi.org/10.1016/j.urology.2006.12.021

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