The Prevalence of Nephrolithiasis in Patients with Primary Gout: A Cross-sectional Study Using Helical Computed Tomography

TORU SHIMIZU and HIROSHI HORI

ABSTRACT. ***Objective.*** To investigate the prevalence of nephrolithiasis in gouty patients by computed tomography (CT) imaging and to compare it with the "prevalence" of urolithiasis calculated from histories of urinary tract calculus.

Methods. The kidneys of 383 male patients with primary gout were examined using an unenhanced 2-row helical CT detector, imaging at 2 mm collimation and a helical pitch of 3. The urolithiasis history of the 383 patients was investigated by inquiry. Patients' ages, body mass index, and laboratory data from a 1-hour clearance test were determined.

Results. CT scans confirmed nephrolithiasis in 103 (26.9%, 95% confidence interval 22.5%–31.6%) of the 383 gouty patients, and history of urinary calculus was positive in 65 (17.0%, 95% confidence interval 13.4%–21.1%) of the 383. However, 64 (62%) of the 103 stone-formers identified by CT had no history of urolithiasis. There was a significant difference between the ages of the 103 stone-formers identified by CT and the 65 stone-formers identified from the history.

Conclusion. The prevalence of nephrolithasis obtained using CT was 26.9% in the 383 patients with primary gout. Our results imply that we cannot determine an accurate prevalence of urolithiasis from a patient's history. Most of the "prevalence" reported in the past may not correspond to a statistically justifiable one, but instead to the "cumulative incidence" during the contraction period of gout. Thus, the prevalence of nephrolithiasis confirmed by a cross-sectional method and the "prevalence" of urolithiasis calculated from patients' calculus histories should be clearly distinguished. (First Release July 15 2009; J Rheumatol 2009;36:1958–62; doi:10.3899/jrheum.081128)

Key Indexing Terms:
GOUT COMPUTED TOMOGRAPHY PREVALENCE
INCIDENCE NEPHROLITHIASIS UROLITHIASIS RENAL CALCULUS

Nephrolithiasis is a clinically important complication of gout, as uric acid metabolism can participate directly or indirectly in the formation of renal stones and may contribute to renal dysfunction. However, the clinical features of this complication remain unclear, and even the prevalence of renal stones in gouty patients has not been precisely evaluated. One reason for this is that until recently no appropriate modality for real-time screening of kidney stones has been available. It is impossible to visualize fine or radiolucent calculi by kidney, ureter, or bladder radiographs. Drip infusion pyelography is complex, requires a long period, and may cause contrast medium-related anaphylaxis. Ultrasonography (US), a noninvasive and low-cost procedure, has been presented as a useful modality for detecting renal stones, even radiolucent ones such as uric acid calculi. However, problems such as diagnostic objectivity and poor image reproducibility remain.

From the Department of Rheumatology and Department of Radiology, Midorigaoka Hospital, Osaka, Japan.

T. Shimizu, MD, Chief, Gout Clinic, Department of Rheumatology; H. Hori, MD, Chief, Department of Radiology, Midorigaoka Hospital.

Address correspondence to Dr. T. Shimizu, Department of Rheumatology, Midorigaoka Hospital, 3-13-1 Makami-cho, Takatsuki-shi, Osaka 569-1121, Japan.

Accepted for pubication April 2, 2009.

Since the original report by Smith, *et al*[1], helical computed tomography (CT) has made great strides. Saw, *et al*[2] and Rimondini, *et al*[3], according to results of a phantom study using a single-row CT detector, concluded that nearly all stones, including those with uric acid components, are visible on 3-mm section collimation combined with a pitch of 1.5 or 2. Memarsadeghi, *et al*[4] concluded from data based on several previous reports that the sensitivities of single-row detector CT scanners range from 96% to 100% and that their specificities range from 92% to 100%. They also stated that no difference was noted between 1.5-mm and 3-mm sections in the detection of calculi, while the sensitivity decreased significantly with 5-mm sections. Since CT has progressed rapidly and become the standard method for screening for urinary tract stones, the CT cross-sectional method can be adjusted for gouty patients to determine the precise prevalence of renal calculi.

MATERIALS AND METHODS

For 6 years (2002-2007), 383 patients were recruited from the gout clinic at Midorigaoka Hospital. They were all male and diagnosed as having primary gout according to the criteria established by the American College of Rheumatology[5]. Within about 1 month after the first visit, the 383 patients were examined for renal stones, with informed consent, using a helical CT scanner with 2-row detectors (Hispeed NX/1; GE Yokogawa Medical Inc., Tokyo, Japan). Imaging was performed without a contrast medium, at 2-mm collimation and a helical pitch of 3. The images were reconstructed at intervals of 3 mm. Axial images, and added coronal sections if necessary, were reviewed using hard copies to search for aberrant high densities in the kidneys. Although the scanner was not very modern, with only a 2-row detector, it was sufficient to provide accurate information on stone size, location, and density for the diagnosis of tiny or radiolucent calculi. In our previous study using this scanner[6], 2 major positive findings with regard to renal stones were observed during CT imaging: a "calculus density spot" in the renal pelvis (Figure 1) and a "high density area" in the renal pyramid (Figure 2). It is reasonable to assume that the calculus density spot in the pelvis was due to a urinary calculus. The high density area observed in the renal pyramid was not identified as a renal calculus. Currently, the high density area is considered to be a normal variation, but the histological characteristics of it remain unclear.

Simultaneously, we investigated the history of urolithiasis in the 383 patients by inquiry. Patients who had experienced spontaneous passing of calculi or received treatment for urinary tract stones and the patients who had had clinical symptoms, such as flank pain or hematuria, and were confirmed as having calculi by US or radiographs were defined as positive for a history of urolithiasis.

To determine the clinical background of the 383 gouty patients, their age, body mass index (BMI), and laboratory data from a 1-hour clearance test including serum uric acid value, serum creatinine value (SCr), creatinine clearance (CCr), uric acid clearance (CUA) and urinary uric acid excretion were examined before the treatment for hyperuricemia began. To clarify differences between the 2 methods of calculating prevalence, variables were compared between the patients with and those without nephrolithiasis categorized by CT findings, and between the patients with and without urolithiasis categorized by urinary calculus history using the t-test. Analysis of covariance (ANCOVA) was used to adjust for age in the comparison of related variables. A p value < 0.05 was considered significant.

RESULTS

In 103 of the 383 gouty patients who underwent unenhanced helical CT, a calculus or calculi were observed in the renal pelvis (Table 1). This means that the prevalence of nephrolithiasis according to cross-sectional analysis was 26.9%. The 95% confidence interval (95% CI) based on the F-distribution of the data ranged from 22.5% to 31.6%.

1a

1b

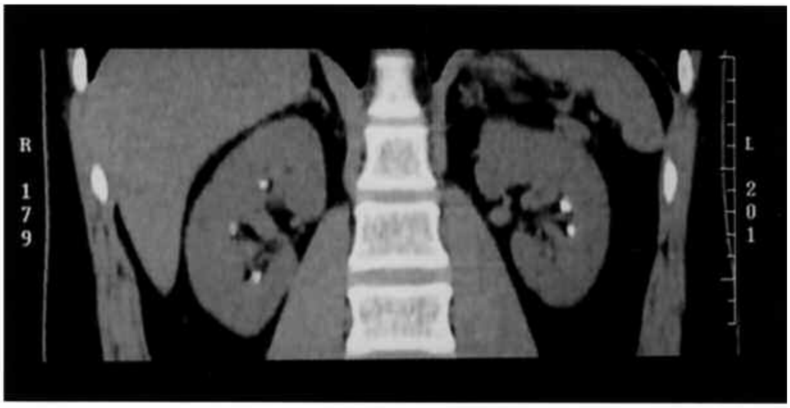

Figure 1. Renal calculi. Axial (a) and coronary CT scans (b) obtained from a 37-year-old man using 140 kV, 300 mA, 2-mm collimation, and a helical pitch of 3, showing calculus density spots in the renal pelvis that were considered to be renal calculi.

2a

2b

2c

Figure 2. High density area in the renal pyramid. CT scans obtained in a 39-year-old man, using 140 kV, 236 mA, at 2-mm collimation, and a helical pitch of 3, showing a high density area in the papillary region of the renal parenchyma (a and b). These findings were considered not to be renal calculi. However, in an ultrasonogram, calculus-like high-echoic spots and hyperechoic regions were noted (c).

Sixty-five of the 383 patients had a history of urolithiasis according to the survey (Table 1). The "prevalence" or positive ratio of urolithiasis in the 383 patients was 17.0%, and the 95% CI based on the F-distribution of the data ranged from 13.4% to 21.1%. Sixty-four of the 103 stone-formers identified on CT examination had no history of urinary tract stones (Table 1). This means 62% of the patients with nephrolithiasis were so-called "silent" stone carriers.

Table 2 and Table 3 show the results of statistical analysis of the variables concerning renal function and uric acid dynamics in the categorized groups. The serum uric acid value of the patients with nephrolithiasis confirmed by CT was significantly higher than that of the patients without nephrolithiasis (Table 2). This suggests that the hyperuricemia of the stone-formers among gouty patients is more severe than that of the non-stone-formers. Significant differences were also noted in the CCr, Cua/CCr, SCr, and BMI between the patients with and those without a history of urolithiasis (Table 3). As CCr deteriorates and SCr rises with age[7], age-related differences presumably contribute to the significance of CCr, Cua/CCr, and SCr. The significance disappeared when we adjusted for age. The significant difference in BMI, on the other hand, increased after the age adjustment (Table 3). This suggests that the gouty patients with a history of urolithiasis have a tendency to obesity.

Table 1. The frequencies of nephrolithiasis diagnosed by CT and urolithiasis diagnosed by stone history in 383 patients with primary gout.

CT Findings	History of Urolithiasis (+)	History of Urolithiasis (–)	Total
Calculus/calculi (+)	39	64	103
Calculus/calculi (–)	26	254	280
Total	65	318	383

Table 2. Comparison of variables between gouty patients with and those without nephrolithiasis on CT examination.

Variables	Patients with Nephrolithiasis on CT, n = 103		Patients without Nephrolithiasis on CT, n = 280		p	p, adjusted for age
	Mean	SD	Mean	SD		
Age, yrs	49.46	12.20	46.76	12.36	0.058	—
Body mass index	24.81	3.11	25.07	3.46	0.501	0.800
SUA, mg/dl	8.84	1.21	8.48	1.17	0.008	0.002*
SCr, mg/dl	0.96	0.18	0.95	0.18	0.577	0.894
CCr, ml/min/1.73m^2	96.33	24.25	99.56	21.98	0.216	0.730
Cua, ml/min/1.73m^2	4.91	1.43	5.21	1.39	0.061	0.374
Cua/CCr (%)	5.21	1.32	5.34	1.39	0.400	0.199
Exua, mg/h	27.78	9.51	28.23	7.80	0.637	0.356

SUA and SCr were measured by an enzymatic method. SUA: Serum uric acid value; SCr: serum creatinine value; CCr: creatinine clearance; Cua: uric acid clearance; Exua: urinary uric acid excretion per hour. * Significant.

Table 3. Comparison of variables between gouty patients with and those without urolithiasis determined by history.

Variables	Patients with Urolithiasis in History, n = 65		Patients without Urolithiasis in History, n = 318		p	p, adjusted for age
	Mean	SD	Mean	SD		
Age, yrs	53.77	11.76	46.20	12.09	< 0.001	—
Body mass index	25.78	3.18	24.84	3.39	0.040	0.003*
SUA, mg/dl	8.66	1.31	8.56	1.16	0.525	0.186
SCr, mg/dl	1.00	0.21	0.94	0.17	0.024	0.630
CCr, ml/min/1.73m^2	90.54	24.28	100.36	21.94	0.001	0.990
Cua, ml/min/1.73m^2	4.95	1.40	5.17	1.40	0.260	0.724
Cua/CCr, %	5.69	1.66	5.23	1.29	0.014	0.209
Exua, mg/h	27.57	8.82	28.22	8.18	0.562	0.072

SUA and SCr were measured by an enzymatic method. SUA: Serum uric acid value; SCr: serum creatinine value; CCr: creatinine clearance; Cua: uric acid clearance; Exua: urinary uric acid excretion per hour. * Significant.

DISCUSSION

Our investigation of 383 patients with primary gout revealed that there was a significant difference between the prevalence of nephrolithiasis confirmed by CT and the "prevalence" of urolithiasis calculated from a stone history (95% CI 22.5%–31.6% vs 13.4%–21.1%, respectively; $p < 0.05$). A significant difference was also noted between the age of the 103 stone-formers identified by CT and that of the 65 stone-formers by history (49.46 ± 12.20 yrs vs 53.77 ± 11.76 yrs, respectively; $p < 0.05$). These findings imply that the 2 kinds of prevalence are fundamentally different and cannot be compared. Further, 62% of the 103 stone-formers identifed by CT had no history of urolithiasis, and 40% of the 65 stone-formers by history were not current stone carriers. This means that we cannot calculate an accurate prevalence of urolithiasis from a history of calculus.

Prevalence is defined as the proportion of patients with a disease at a specific timepoint. Examination of the kidneys using CT at the first visit to hospital is warranted as part of a cross-sectional approach to determine a definitive prevalence of nephrolithiasis. Yu and Gutman[8], Fessel[9], and Kramer and Curhan[10] reported that the prevalence of urolithiasis in gouty patients was 22%, 15%, and 13.9%, respectively. These values, however, were calculated using urolithiasis histories, and no cross-sectional method was employed. These values may not correspond to an accurate prevalence, but instead to the "cumulative incidence" in the contraction period of gout. The term "incidence" represents the number of patients with the onset of a condition (or disease) in a population over a specific period of observation. Alvarez-Nemegyei, *et al*[11] reported that 39% of 140 gouty patients had urolithiasis, of which 26% were diagnosed by their clinical history and 13% by US. In their report, 2 analytic methods, which should have been distinguished, were used together.

The use of the 2 terms prevalence and incidence is sometimes confusing. For example, there is a well known study that reported that the prevalence of uric acid urolithiasis among gouty patients is of an order 1000 times greater than in the non-gouty population[8]. Upon checking the report, we found that this "1000 times" was calculated by comparing the prevalence in gouty patients with the annual incidence in the general population[12]. Therefore, "1000 times" seems to be inaccurate.

Cross-sectional investigation of the prevalence of nephrolithiasis is also possible by using US along with CT. Okabe, *et al*[13] examined 172 male patients with gout using US and recognized stone formation in 52 (30.2%) of them. However, discrepancies are occasionally noted in the diagnostic results of renal calculi between US and CT. In some instances, CT confirmed tiny stones in the renal pelvis, although US could not detect them. In contrast, there were cases in which US revealed a calculus-like echo with an acoustic shadow, but on CT the calculus could not be found. The authors suggest that the results of diagnosis with CT concerning stone number, location, and size are much more reliable than the results obtained with US.

Recently, the development of multidetector helical CT has increased scanning speed and made the real-time screening of renal calculi easier. In the urological field, the target for treatment and examination is usually symptomatic urolithiasis. In gouty patients, however, even silent stones should not be neglected because hyperuricemia, hyperuricosuria, or acidic urine can create a higher risk for new formation or multiplication of renal calculi. Objective images can be recorded and stored, allowing serial monitoring from the first development to the disappearance of calculi even in the silent stage. As therapeutic strategies for hyperuricemia are adjusted according to the calculi components, it is also important to clarify the stone components in gouty patients. When the region of interest is extensive, the components of calculi can be estimated using attenuation differences[2]. Thus, for hyperuricemic or gouty patients, kidney screening with multidetector helical CT constitutes a precautionary approach to renal complications caused by the metabolic disturbance of uric acid.

REFERENCES

1. Smith RC, Rosenfield AT, Choe KA, et al. Acute flank pain: comparison of non-contrast-enhanced CT and intravenous urography. Radiology 1995;194:789-94.
2. Saw KC, McAteer JA, Monga AG, Chua GT, Lingeman JE, Williams JC Jr. Helical CT of urinary calculi: Effect of stone composition, stone size, and scan collimation. AJR Am J Roentgenol 2000;175:329-32.
3. Rimondini A, Pozzi Mucelli R, De Denaro M, Bregant P, Dalla Parma L. Evaluation of image quality and dose in renal colic: Comparison of different spiral-CT protocols. Eur Radiol 2001;11:1140-6.
4. Memarsadeghi M, Heinz-Peer G, Helbich TH, et al. Unenhanced multi-detector row CT in patients suspected of having urinary stone disease: Effect of section width on diagnosis. Radiology 2005;235:530-6.
5. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900.
6. Shimizu T, Imanishi T, Kato H, Hori H, Mikami Y. Studies on renal calculi complicating primary gout by non-enhanced helical CT [Japanese]. Gout Nucleic Acid Metabolism 2002;26:137-41.
7. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men: A cross-sectional and longitudinal study. J Gerontology 1976;31:155-63.
8. Yu TF, Gutman AB. Uric acid nephrolithiasis in gout. Predisposing factors. Ann Intern Med 1967;67:1133-48.
9. Fessel WJ. Renal outcomes of gout and hyperuricemia. Am J Med 1979;67:74-82.
10. Kramer M, Curhan G. The association between gout and nephrolithiasis: The National Health and Nutrition Examination Survey, 1988-1994. Am J Kidney Dis 2002;40:37-42.
11. Alvarez-Nemegyei J, Medina-Escobedo M, Villanueva-Jorge S, Vazquez-Mellado J. Prevalence and risk factors for urolithiasis in primary gout: is reappraisal needed? J Rheumatol 2005;32:2189-91.
12. Boyce WH, Garvey FK. Incidence of urinary calculi among patients in general hospitals, 1948 to 1952. JAMA 1956;161:1437-42.
13. Okabe H, Hosoya T, Hikita M, Saji M, Ichida K, Ohno I. Analysis of urolithiasis in patients with gout and hyperuricemia using ultrasonography. Jpn J Rheumatol 1999;9:239-44.