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ORIGINAL ARTICLE

Prevalence and clinical association of hyperechoic crystal deposits on ultrasonography in patients with chronic kidney disease: a cross-sectional study from a single center

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Abstract

Background Hyperechoic crystal deposits can be detected in the kidney medulla of patients with gout by ultrasonography examination. Chronic kidney disease (CKD) is usually accompanied with hyperuricemia. Whether hyperechoic crystal deposition could be detected by ultrasonography in CKD patients, and its clinical association are unknown.

Methods Five hundred and fifteen consecutive CKD patients were included in this observational study. Clinical, biochemical and pathological data were collected and analyzed.

Results Altogether, 234 (45.4%) patients were found to have hyperuricemia and 25 patients (4.9%) had gout history. Hyperechoic crystal deposits in kidney medulla were found in forty-four (8.5%) patients, on ultrasonography. Compared with patients without hyperechoic crystal deposits, patients with deposits were more likely to be male, younger, with gout history and presenting with higher serum uric acid level, lower estimated glomerular filtration rate, lower urine pH, lower 24 h-urinary citrate and uric acid excretion, and with a higher percentage of ischemic nephropathy (all $p < 0.05$). On multivariable logistic analysis, the hyperechoic depositions were associated with age [0.969 (0.944, 0.994), $p = 0.016$], serum uric acid level [1.246 (1.027, 1.511), $p = 0.026$], Sqrt-transformed 24 h-urine uric acid excretion [0.923 (0.856, 0.996), $p = 0.039$], and ischemic nephropathy [4.524 (1.437, 14.239), $p = 0.01$], respectively.

Conclusions Hyperechoic crystal deposition can be detected in kidney medulla by ultrasonography; in CKD patients their presence was associated with hyperuricemia as well as with ischemic nephropathy.

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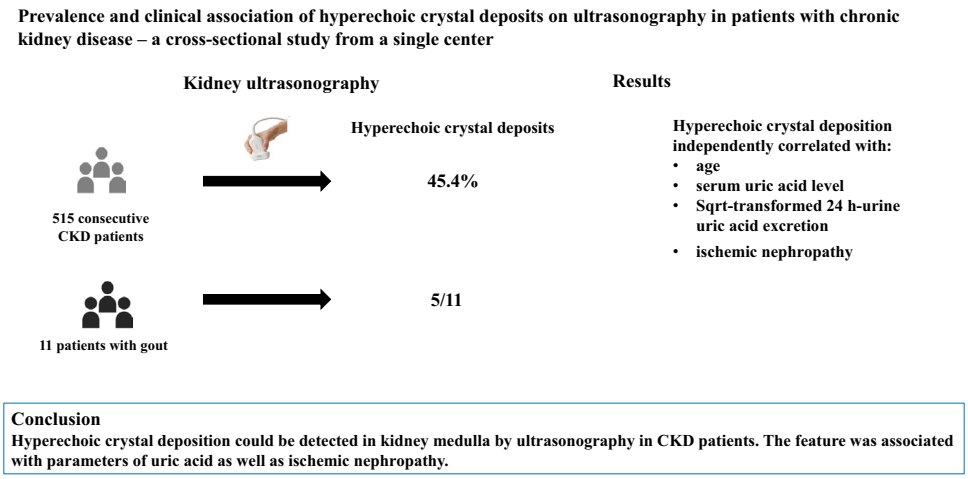
Graphical abstract



Keywords Renal ultrasonography · Chronic kidney disease · Hyperuricemia · Microcrystalline nephropathy

Introduction

The kidneys play an important role in the regulation of uric acid by excreting approximately two-thirds of the body's uric acid load daily [1, 2]. Defective renal handling of uric acid, through reduced glomerular filtration rate, enhanced reabsorption or insufficient tubular secretion, leads to hyperuricemia, a common finding in chronic kidney disease (CKD) [3]. It is suggested that even asymptomatic hyperuricemia contributes to the progression of the kidney disease through the systemic and local effects exerted by urate [4–11]. However, the results of interventional studies involving the use of urate-lowering drugs to slow-down the progression of kidney disease are inconsistent [12–16]. Microcrystalline nephropathy with the deposition of monosodium urate or uric acid crystals in the kidney is believed to play a critical role in hyperuricemia-induced renal impairment [17–20]. As shown by Sellmayer et al., asymptomatic hyperuricemia alone did not cause or drive the progression of CKD. Only hyperuricemia with uric acid crystal formation/deposition contributed to CKD progression by causing tubular obstruction, interstitial inflammatory changes, including infiltration of inflammatory cells, giant cell granuloma formation, and interstitial fibrosis [20]. This result supported the role of uric acid crystal deposition as an indicator for potential urate-lowering therapy.

Uric acid crystal usually deposits in kidney medulla [21, 22]. It is rare to find uric acid deposition in renal biopsies, which mainly consist of kidney cortex. Ultrasonography examination has proven to be useful for the detection of hyperechoic crystal deposition, especially when combined with the feature of twinkling artifacts observed on color Doppler ultrasonography [23–26]. In a recent study, hyperechoic kidney medulla with twinkling artifacts on color Doppler ultrasonography were found in 36% of 502 patients with untreated gout. The ultrasonography features were associated with heavy uric acid burden. Interestingly, the researchers observed the disappearance of the hyperechoic kidney medulla in a few patients who underwent intensive urate-lowering treatment [27]. This finding suggested the possibility of ultrasonography examination as a method for detection of uric acid crystal deposits.

In the present study, we investigated the frequency of hyperechoic crystal deposition detection in the renal medulla by ultrasonography and its correlation with clinical, biochemical and pathological findings in a large cohort of Chinese patients with CKD. Results of renal ultrasonography performed at the same institution in patients with gout were also analyzed, in an attempt to validate our findings.

Methods

Study population

We prospectively selected consecutive adult patients (> 18 years) who underwent renal biopsy at the Renal Division, Peking University First Hospital between January 2021 and January 2022. Patients were excluded according to the following criteria: patients who received renal replacement therapy before admission, and those with severe heart or liver dysfunction and infection, established malignancy with chemotherapy in the previous 2 weeks, urine volume less than 800 ml *per* day, and incomplete 24 h-urine collection.

Altogether, 515 CKD patients were included in the present analysis. Eleven patients with established gout who underwent kidney ultrasonography examination were recruited as controls. This study was approved by the committee of Ethics of the Peking University First Hospital (approval number: 2021–236) and performed in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient at kidney biopsy.

Data collection

Demographic data (age, gender), medical history (hypertension, diabetes, gout, urolithiasis, coronary heart disease), and biological data (body mass index [BMI]) were collected. Laboratory data of serum (creatinine, albumin, uric acid, calcium, phosphorus, bicarbonate) and urinalysis (morning urine pH, 24 h-urinary excretion of calcium, phosphorus, magnesium, oxalate, citrate and uric acid, 24 h-urinary protein excretion, 24 h urine volume [24 h-UV]) at the time of renal biopsy were also collected. Information concerning medication use at admission including urate-lowering agents (such as allopurinol, febuxostat, benzbromarone), corticosteroids, diuretics, calcium supplement and vitamin D were recorded. Pathological diagnosis was recorded and categorized into glomerular disease, tubulointerstitial nephritis and ischemic nephropathy according to the primary finding on renal biopsy. The oxalate and citrate measurement was performed by Aquion RFIC (Thermo Fisher Scientific, USA). eGFR was estimated by the CKD-EPI equation. According to the Kidney Disease: Improving Global Outcomes CKD guidelines, the patients were divided into the G1 group (eGFR $\geq$ 90 ml/ min/1.73 m^2), G2 group (60 $\leq$ eGFR < 90 ml/ min/1.73 m^2), G3 group (30 $\leq$ eGFR < 60 ml/min/1.73 m^2), G4 group (15 $\leq$ eGFR < 30 ml/min/1.73 m^2) and G5 group (eGFR < 15 ml/min/1.73 m^2). Serum corrected calcium level (mmol/L) was calculated using correction formula: measured serum calcium level (mmol/L) + 0.02 × (40-serum albumin level) (g/L). Hyperuricemia was defined as the serum level of uric acid > 7 mg/dl. Urinary uric acid represented 24-h uric acid, which was calculated as urine uric acid concentration × 24 h-UV. Urine uric acid was categorized into 3 groups: < 250 mg/day, 250-750 mg/day, > 750 mg/day, respectively. Hyperuricosuria was defined as urine uric acid of over 750 mg/day.

Imaging procedure

The ultrasonography examination of the kidneys was performed using the lower broadband convex transducer C5-1 (Philips EPIQ5, Philips US, Inc., Bothell, Washington, USA) and PVT-375BT (Canon Aplio 500, Canon Medical Systems Corporation, Otawara, Japan) for abdominal imaging. Crystal deposition in the renal medulla was diagnosed when hyperechogenicity of renal medulla with bright echogenic foci were found on grey-scale ultrasonography, and/or when twinkling artifacts were found on color Doppler ultrasonography with appropriate settings. The diagnosis of crystal deposition was made by two sonographers independently who were blinded to the clinical and pathological data of each patient.

Statistical analysis

Quantitative data are presented as median with interquartile range (IQR), means with standard deviations (SD), and categorical data by number (%). Groups were compared by Wilcoxon rank sum and Student's *t*-test for quantitative and Fisher exact tests for categorical characteristics, respectively. A multivariable logistic model was used to assess the association between patient characteristics and presence of hyperechoic crystal deposition of the renal medulla. All variables significant at $p < 0.05$ on univariate analysis were included in the multivariable model. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Urine uric acid was Sqrt-transformed due to the significant skewness. The primary analysis was performed with complete cases. Sensitivity analysis was performed with exclusion of the patients who were taking urate-lowering agents at admission. All tests were 2-sided, with $p < 0.05$ considered statistically significant. Analyses were performed with SPSS (version 22.0, IBM corporation).

Results

The main characteristics of the 515 consecutive CKD patients considered in the study are shown in Table 1. Fifty-seven percent (291/515) of patients were males, with a mean age of 46.3 (14.6) years. In total, 25 (4.9%) patients reported gout history, and 43 (8.3%) patients were on urate-lowering therapy at admission. Overall, 13 (2.5%) patients had a history of urolithiasis, 97 (18.8%) were diabetic, 294 (57.1%) had hypertension and 27 (5.1%) had a diagnosis of coronary heart disease. The mean eGFR was 64.3 (33.4) ml/ min/1.73 m^2, and the number and percentage of patients with CKD stages G1, G2, G3, G4, and G5 were 146 (28.3%), 126 (24.5%), 137 (26.6%), 67 (13.0%) and 39 (7.6%), respectively. Mean serum uric acid was 6.8 (1.8) mg/dL, with 234 (45.4%) patients having hyperuricemia. The proportion of patients with hyperuricemia increased in accordance with the progressing CKD category (Fig. 1A). The median level of urine uric acid was 296.7 (203.8, 427.8) mg/24 h. There were 6 (1.2%) patients with hyperuricosuria, 2 of whom also had hyperuricemia. About one third (189/515, 36.7%) of the patients presented with urine uric acid less than 250 mg/d, with 95 (50.3%) patients also having hyperuricemia. The

Table 1 Main characteristics of the patients with and without hyperechoic deposition in renal medulla on ultrasonography

	Whole cohort	With hyperechoic deposition on ultrasonography	w/o hyperechoic deposition on ultrasonography	*p*
Case number	515	44	471	–
Male, *n* (%)	291 (56.5)	33 (75.0)	258 (54.8)	0.011
Age, years	46.3 (14.6)	41.9 (13.2)	46.7 (14.7)	0.041
BMI, kg/m^2	24.9 (3.9)	25.4 (3.9)	24.9 (3.9)	0.398
Hypertension, *n* (%)	294 (57.1)	28 (63.6)	266 (56.5)	0.427
Diabetes, *n* (%)	97 (18.8)	8 (18.2)	89 (18.9)	0.908
Gout, *n* (%)	25 (4.9)	6 (13.6)	19 (4.0)	0.014
Coronary heart disease, *n* (%)	27 (5.1)	3 (6.0)	24 (5.0)	0.734
Urolithiasis, *n* (%)	13 (2.5)	3 (6.8)	10 (2.1)	0.091
Diuretic, *n* (%)	122 (23.7)	7 (15.9)	115 (24.4)	0.266
Urate lowing therapy, *n* (%)	43 (8.3)	6 (13.7)	37 (7.9)	0.246
Corticosteroids, *n* (%)	84 (16.3)	6 (13.6)	78 (16.6)	0.831
Calcium supplement, *n* (%)	67 (13.0)	3 (6.8)	64 (13.6)	0.248
Vitamin D supplement, *n* (%)	81 (15.7)	5 (11.4)	76 (16.1)	0.519
eGFR, ml/min/1.73 m^2	64.3 (33.4)	49.3 (26.4)	65.7 (33.7)	< 0.001
CKD stage				0.002
G1	146 (28.3)	5 (11.4)	141 (29.9)	
G2	126 (24.5)	7 (15.9)	119 (25.3)	
G3	137 (26.6)	20 (45.5)	117 (24.8)	
G4	67 (13.0)	10 (22.7)	57 (12.1)	
G5	39 (7.6)	2 (4.5)	37 (7.9)	
Serum uric acid, mg/dL	6.8 (1.8)	7.9 (1.9)	6.7 (1.8)	< 0.001
Hyperuricemia, n (%)	234 (45.4)	30 (68.2)	204 (43.3)	0.002
Calcium, mmol/L	2.39 (0.10)	2.40 (0.09)	2.39 (0.10)	0.338
Phosphorous, mmo/L	1.17 (0.25)	1.14 (0.26)	1.17 (0.25)	0.441
Bicarbonate, mmol/L	25.8 (3.0)	25.4 (2.7)	25.8 (3.1)	0.4
Urine pH	6.1 (0.6)	5.9 (0.5)	6.1 (0.6)	0.018
Urine volume, ml	1995 (701)	1990 (635)	1996 (708)	0.959
Urine protein, g/d	1.89 (0.82, 4.23)	1.67 (1.06, 3.92)	1.92 (0.80, 4.38)	0.904
24 h-urinary uric acid excretion, mg	296.7 (203.8, 427.8)	222.5 (137.3, 340.2)	299.1 (205.4, 432.8)	0.003
24 h-urinary Ox excretion, mg	15.3 (11.7, 18.9)	12.6 (9.0, 17.8)	15.3 (11.7, 19.8)	0.054
24 h-urinary Cit excretion, mg	198 (167)	136 (96)	204 (171)	< 0.001
24 h-urinary Ca excretion, mmol	1.32 (0.55, 2.50)	1.04 (0.44, 2.10)	1.33 (0.55, 2.54)	0.109
24 h-urinary P excretion, mmol	14.6 (10.4, 19.6)	13.8 (9.1, 18.2)	14.7 (10.6, 19.6)	0.295
24 h-urinary Mg excretion, mmol	2.8 (2.1, 3.8)	2.7 (2.1, 3.2)	2.8 (2.0, 3.8)	0.285
Renal pathology				0.008
Glomerulopathy, *n* (%)	462 (89.7)	35 (79.5)	427 (90.7)	
Tubulointerstitial nephritis, *n* (%)	30 (5.8)	3 (6.8)	27 (5.7)	
Ischemic nephropathy, *n* (%)	23 (4.5)	6 (13.6)	17 (3.6)	

Data presented as mean (standard deviation, SD) or median (interquartile range, IQR) or percentage

BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; Ox, oxalate; Cit, citrate; Ca, calcium; P, phosphorous; Mg, magnesium

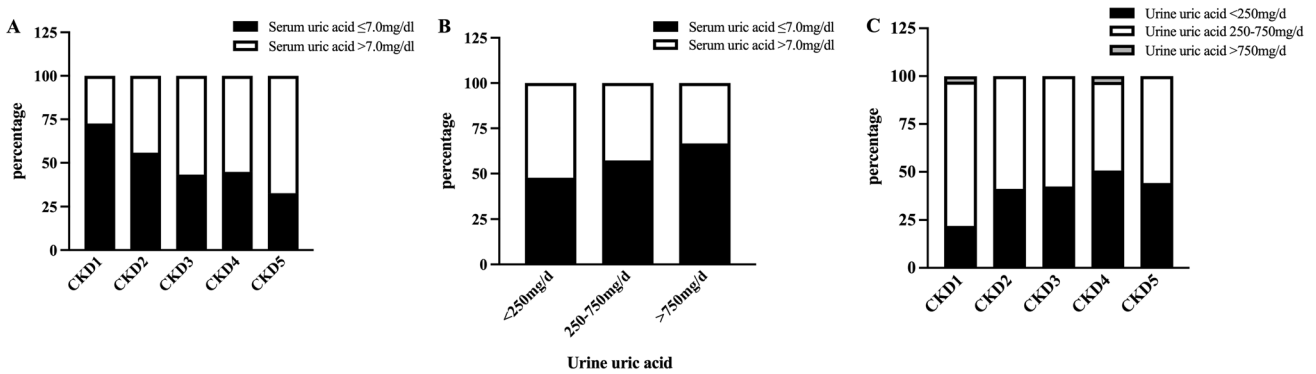


Fig. 1 **A** Distribution of hyperuricemia according to CKD stages; **B** distribution of hyperuricemia according to urine uric acid categories; **C** distribution of urine uric acid categories according to CKD stages. Hyperuricemia was defined as the serum level of uric acid >7mg/dl

proportion of hyperuricemia according to urine uric acid category is shown in Fig. 1B. The distribution of urine uric acid category according to CKD stage is shown in Fig. 1C.

In 44/515 (8.5%) patients, renal ultrasonography revealed hyperechoic crystal deposits in kidney medulla (Fig. 2A), which presented as twinkling artifacts on color Doppler ultrasonography (Fig. 2B). The prevalence of hyperechoic crystal deposits was comparable between patients with (6/43, 14.0%) and without urate-lowering therapy (38/472, 8.1%) ($p = 0.246$). Compared with patients without crystal deposits, patients with hyperechoic crystal deposits were more likely to be male, younger, and with gout history (all $p < 0.05$). No significant difference in previous history of urolithiasis and current medication use was found between the patients with and without hyperechoic crystal deposits. Patients with hyperechoic crystal deposits had lower eGFR and higher serum uric acid level (both $p < 0.001$). We further compared the urinary indices, which might be involved in the crystal formation between the patients with and without hyperechoic crystal deposits. Patients with crystal deposition presented with significantly lower morning urine pH ($p = 0.018$), 24 h-urinary excretion of citrate ($p < 0.001$) and uric acid ($p = 0.003$). No significant difference in 24 h-UV and 24 h-urinary excretion of protein, calcium, phosphate, magnesium and oxalate was found.

All patients underwent renal biopsy. There were 427 patients (90.5%) with primary or secondary glomerular nephritis as the primary pathologic diagnosis, including membranous nephropathy, focal segmental glomerular sclerosis, membranous proliferative glomerular nephritis, IgA nephropathy, amyloidosis, lupus nephritis, etc. Furthermore, 28 patients (5.9%) were diagnosed with tubulointerstitial nephropathy, of whom 17 (3.6%) with a diagnosis of ischemic nephropathy. The distribution of pathological changes differed between patients with and without hyperechoic crystal deposition ($p = 0.008$), with a higher percentage of ischemic nephropathy found in patients with hyperechoic crystal deposition (Table 1). We reviewed the renal biopsies of the 44 patients with hyperechoic crystal deposits on ultrasonography. Twenty-one samples (21/44, 47.7%) contained medulla tissue in the specimen, and 3 (3/21, 14.3%) of them were found with evidence of uric acid crystal deposition and/or granuloma formation (Fig. 3). Detailed information of the 3 patients is presented in Supplemental Table 1.

The correlation of demographic, clinical and pathological features with hyperechoic crystal deposits on ultrasonography was analyzed by Logistical regression analysis. The results of univariate and multivariable analysis are summarized in Table 2. Age [0.969 (0.944, 0.994), $p = 0.016$], serum uric acid level [1.246 (1.027, 1.511),

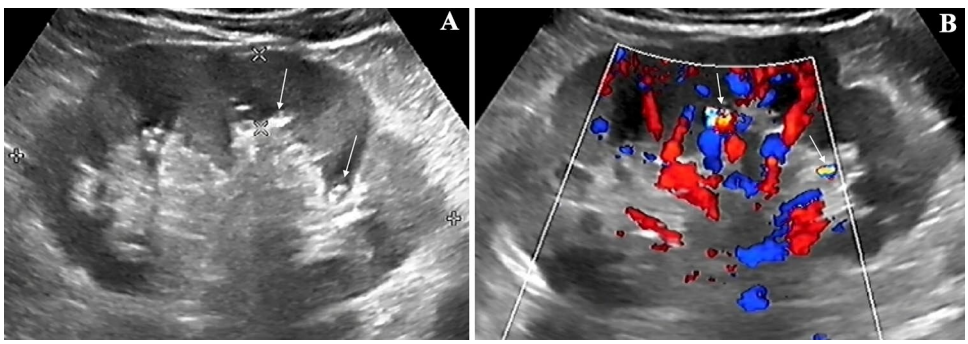


Fig. 2 **A** Hyperechoic deposits in renal medulla on B-mode ultrasonography. **B** Color-Doppler ultrasonography exhibiting twinkling artifacts

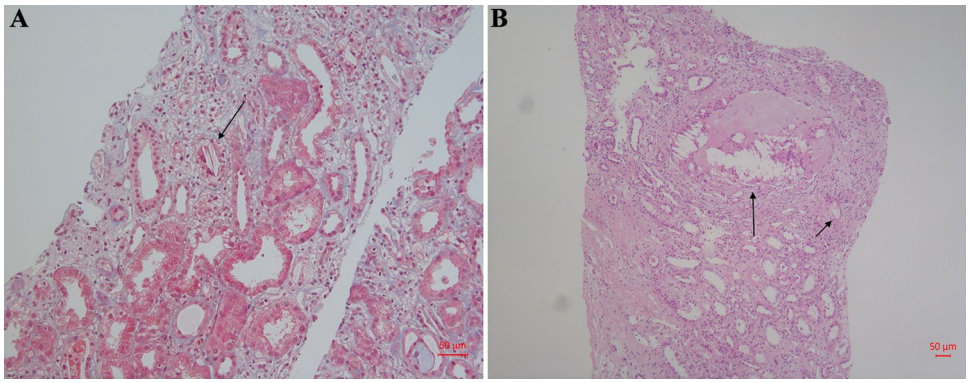


Fig. 3 Pathological features of uric acid crystal deposition in renal biopsies. **A** Intratubular uric acid crystal deposition (Pt. 2). The uric acid crystals are dissolved and appear as empty spaces. (Masson trichrome stain × 200); **B** uric acid granuloma formation in the medulla (Pt. 3). The lesion is characterized by clear, feathery central areas (mostly dissolved uric acid crystals) with peripheral inflammatory reactions. (HE stain × 100)

Table 2 Univariate and Multivariate analysis of the correlation of clinic-pathological features with hyperechoic deposition in renal medulla on ultrasonography

	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex	0.404 (0.199, 0.818)	**0.012**	0.507 (0.228, 1.128)	0.096
Age	0.977 (0.956, 0.999)	**0.043**	0.969 (0.944, 0.994)	**0.016**
Gout	3.756 (1.416, 9.965)	**0.008**	1.903 (0.628, 5.772)	0.255
Urolithiasis history	3.373 (0.893, 12.743)	0.073	–	–
eGFR, ml/min/1.73 m^2	0.985 (0.975, 0.995)	**0.002**	0.992 (0.980, 1.005)	0.22
Serum uric acid, mg/dL	1.400 (1.188, 1.651)	**< 0.001**	1.246 (1.027, 1.511)	**0.026**
Bicarbonate, mmol/L	0.958 (0.867, 1.058)	0.399	–	–
Urine pH	0.491 (0.271, 0.887)	**0.018**	0.820 (0.407, 1.651)	0.578
Urine volume, ml	1.000 (1.000, 1.000)	0.958	–	–
Sqrt_ 24 h-urinary uric acid excretion, mg	0.958 (0.933, 0.984)	**0.002**	0.923 (0.856, 0.996)	**0.039**
Sqrt_24 h-urinary Ox excretion, mg	0.712 (0.510, 0.995)	**0.046**	0.716 (0.488,1.051)	0.088
24 h-urinary Cit excretion, mg	0.997 (0.994, 0.999)	**0.011**	0.998 (0.995, 1.001)	0.196
Sqrt_24 h-urinary Ca excretion, mmol	0.568 (0.314, 1.029)	0.062	–	–
Sqrt_24 h-urinary P excretion, mmol	0.841 (0.601, 1.176)	0.31	–	–
Sqrt_24 h-urinary Mg excretion, mmol	0.606 (0.275, 1.337)	0.215	–	–
Renal pathology				
Glomerulopathy	1		1	
Tubulointerstitial nephritis	1.356 (0.392, 4.692)	0.631	1.991 (0.475, 8.336)	0.346
Ischemic nephropathy	4.306 (1.596, 11.617)	**0.004**	4.524 (1.437, 14.239)	**0.01**

OR odds ratio, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *Ox* oxalate, *Cit* citrate, *Ca* calcium, *P* phosphorous, *Mg* magnesium

All variables significant at $p < 0.05$ on univariate analysis were included in the multivariable model

Bold identifies *p* value statistically significant

$p = 0.026$], Sqrt-transformed 24 h-urine uric acid excretion [0.923 (0.856, 0.996), $p = 0.039$], and ischemic nephropathy [4.524 (1.437, 14.239), $p = 0.01$] were associated with hyperechoic crystal deposition in the renal medulla. Sensitivity analysis with the exclusion of 43 cases on urate-lowering treatment showed similar results with serum uric acid level [1.290 (1.036, 1.605), $p = 0.023$] and Sqrt-transformed 24 h-urine uric acid excretion [0.922 (0.853, 0.996), $p = 0.039$] being significantly associated with renal medullary hyperechoic crystal deposition on multivariable analysis (Supplemental Table 2).

We also collected the data of 11 out-patients with established gout who underwent kidney ultrasonography examination in our ultrasonography center (Table 3). Hyperechoic crystal depositions, presenting as twinkling

Table 3 Main features of 11 patients with gout undergoing ultrasonography examination

	With hyperechoic deposition on ultrasonography	w/o hyperechoic deposition on ultrasonography
Case number	5	6
Male, *n* (%)	5 (100)	6 (100)
Mean age, years	34.8	40.3
Mean serum uric acid, mg/dL	9.1	7.2
Hyperuricemia, *n* (%)	4 (80)	3 (50)
Mean serum creatinine, μmol/L	84.4	92.5
Mean eGFR, ml/min/1.73 m^2	102.1	89.1
Mean urine pH	5.7	5.7

eGFR estimated glomerular filtration rate

artifacts on color Doppler ultrasonography, were observed in 5 patients (Supplemental Fig. 1).

Discussion

In the present cross-sectional study, we identified 44 patients with hyperechoic crystal deposition in renal medulla on ultrasonography in a cohort of 515 Chinese patients with CKD. The finding was mainly observed in patients with hyperuricemia and low urinary uric acid excretion, and was associated with ischemic nephropathy.

Nearly half of our patients with CKD presented with asymptomatic hyperuricemia. Whether asymptomatic hyperuricemia contributes to the progression of CKD remains a subject of debate. It is proposed that the contribution of hyperuricemia to CKD progression depends on the formation and deposition of uric acid crystals in the kidney, which cause tubular obstruction, interstitial inflammation and fibrosis [17–20]. However, the deposition of urate crystals usually occurs in the renal medulla and is difficult to observe in renal biopsy specimens due to insufficient sampling of medulla for obvious safety concerns related to the procedure. In a previous study by Ayoub et al., who reviewed renal biopsies containing mostly or exclusively medulla, medullary tophi were found in 35 samples of 572 CKD patients [22].

In a recent study, Bardin et al. observed hyperechoic kidney medulla with twinkling artifacts on ultrasonography in about 36% of a large series of Vietnamese gout patients. The finding was mainly observed in gout patients with heavy crystal load, suggesting that the ultrasonography picture could be a feature of urate microcrystalline deposition in the kidneys [27]. We found similar features in 5 out of 11 gout patients who underwent ultrasonography examination in our center. With the same ultrasonography device and parameter setting, we detected hyperechoic deposits in kidney medulla in 44 (8.5%) out of 515 CKD patients. Although the nature of the crystal responsible for the hyperechoic deposits could not be definitively ascertained, several lines of evidence suggest they may be urate/uric acid crystals. First, uric acid crystal deposition and granuloma were found in 3 out of 21 patients with ultrasonography-positive findings whose renal biopsy samples contained medullary tissue. Second, gout history, hyperuricemia, low urine pH and low urine citrate and uric acid excretion, which favor uric crystal formation, were observed more often in patients with hyperechoic deposits in the medulla. After multiple adjustments, the picture remained associated with hyperuricemia and low uric acid excretion. Furthermore, we measured urine excretion of calcium, phosphate, and oxalate, which are involved in the formation of other types of crystal/stones, but no significant difference was found between patients with or without hyperechoic deposits in the present study. Taken together, we propose that the hyperechoic images found in kidney medulla are a feature suggestive of urate/uric acid crystal deposition in our CKD patients.

The causes of CKD in the present study were diverse as demonstrated by renal biopsy. Interestingly, hyperechoic deposits in the kidney medulla were associated with ischemic nephropathy both in univariate and multivariate analysis. Hyperuricemia was found to be related to renal arteriosclerosis in patients with kidney disease and in population-based autopsy samples [28–30]. In a study by Russo et al., serum urine acid was found to be significantly associated with arteriolar damage at the renal biopsy in 145 patients with biopsy-proven IgA nephropathy [28]. In a study by Kohagura et al., hyperuricemia was significantly associated with a higher risk of renal arteriolar damage in 167 patients with CKD who underwent renal biopsy [29]. A similar finding was reported in a study with 547 population-based autopsy samples [30]. In this study, elevated uric acid levels were significantly associated with advanced kidney arteriosclerosis. It has been reported that hyperuricemia was associated with similar vascular lesions of the kidneys in rodents [31]. Interestingly, however, in the present study, the hyperechoic deposits in the kidney

medulla were not associated with hypertension on univariable analysis. Due to the cross-sectional nature of the study, the relationship between uric acid and ischemic nephropathy requires further studies.

Our study has some limitations. Firstly, the patients did not receive dual energy computed tomography examination to verify the uric acid crystal deposition. Secondly, the nature of the study makes it hard to determine any causal relationship. Thirdly, urinary excretion of the different electrolytes was measured only once, and the variability of the measure could not be taken into account. Finally, we only enrolled patients who underwent a renal biopsy. Whether our findings are applicable to the overall population with established CKD who do not undergo renal biopsy needs further study. Nonetheless, our study also has its strengths. We enrolled a large number of consecutive CKD patients with complete clinical, imaging and pathological data. Furthermore, the data were collected prospectively and missing data were few.

In conclusion, our findings showed that hyperechoic crystal deposition in kidney medulla can be observed by ultrasonography in CKD patients. The deposition was associated with parameters suggestive of uric acid metabolic derangements as well as with ischemic nephropathy. This ultrasonography feature may be taken as a tool to focus further examinations on deposition of uric acid crystal in the kidneys of CKD patients in order to evaluate potential administration of urate-lowering therapy.

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Data availability statement The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest The authors state they have no conflict of interest for this manuscript.

Ethical approval This study was approved by the committee of Ethics of the Peking University First Hospital (approval number: 2021-236).

Statement of Human and Animal Rights This article contains study with human participants. The study was performed in accordance with the Declaration of Helsinki.

Informed consent Informed consent was obtained from each patient at kidney biopsy.

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