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BIOMEDICAL SCIENCE IN BRIEF

Fasting urinary calcium to creatinine ratio for the evaluation of calcium nephrolithiasis in adults

Lijing Sun[a,b], Zhiyong Guo[b], Jianping Shan[a] and Gengru Jiang[a]

[a]Department of Nephrology, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China; [b]Department of Nephrology, Changhai Hospital Affiliated to Second Military Medicial University, Shanghai, China

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Calcium has many important roles in physiology and pathology, such as in ensuring bone integrity, in maintaining haemostasis, and as a cofactor for metabolic enzymes. The kidney is the major organ responsible for blood calcium homeostasis and ideally maintains plasma levels under tight control through urinary excretion.[1] Accordingly, changes in urinary calcium excretion are likely to reflect alterations in homoeostasis. Levels of urinary calcium vary widely in different populations as a result of dietary habits, mineral composition of water, climate, genetics and race.[2] Hypercalciuria is a common clinical finding, which increases the risk of renal stones, principally calcium nephrolithiasis. In China, nephrolithiasis is a common condition with a lifetime prevalence of 4.8% in men and 3% in women.[3]

The current gold standard criteria for diagnosing hypercalciuria is urinary calcium excretion >4 mg/kg/24 h or >300 mg/24 h in men and >250 mg/24 h in women and is likely to be a directly relevant diagnostic test for calcium nephrolithiasis. Although urinary calcium excretion is best measured by a 24-h collection, this is not always suitable or practical as a test because of difficulties in sample collection and leading to invalid results. An alternative, the urinary calcium/creatinine (UCa/Cr) ratio is often used in this circumstance instead of a 24-h sample collection. Nordin first proposed the UCa/Cr ratio as a measure of urinary calcium excretion,[4] and although some studies showed a strong correlation between UCa/Cr ratio and 24 h urinary calcium excretion, two studies reported opposite result.[5,6] Consequently, the replacement of the 24-h urinary calcium excretion method with the UCa/Cr ratio is controversial and requires clarification.

Most studies focus on UCa/Cr ratio in paediatric populations: data on adult UCa/Cr ratio (especially in calcium nephrolithiasis) limited. Our study was initiated to determine the value of UCa/Cr ratio in discriminating normal adults from patients with calcium nephrolithiasis, and to determine the effects of factors that may influence the UCa/Cr ratio. We tested the primary hypothesis that the UCa/Cr ratio correlates significantly with 24-h urinary calcium excretion in healthy controls and in patients with nephrolithiasis.

This prospective study included 120 healthy volunteers and 120 nephrolithiasis patients. The participants selected were in the period between November 2011 and November 2014. The calcium nephrolithiasis patients with only one stone episode were diagnosed based on the clinical findings (medical history, physical examination, chemical composition analysis of nephrolithiasis, radiography and ultrasound). Exclusion criteria were patients with renal tubular acidosis, congenital bone disease, hyperparathyroidism, inflammatory bowel disease, those who were treated with bisphosphonates, calcium, vitamin D, steroids and diuretics were also excluded. The study performed according to the Declaration of Helsinki and was approved by the ethics committee of our hospital, all of the participants gave informed consent and took a standard Chinese diet.

First morning fasting urine samples were obtained for calcium, creatinine, albuminuria, pH and density. 24-h urine samples were analysed for urinary calcium excretion. Serum urea, creatinine, electrolytes, urinary calcium and albuminuria were determined by a Hitachi 7600 biochemistry analyser (Hitachi, Japan), urine PH and density were determined by Urisys 2400 analyser (Roche, Switzerland). Body mass index (BMI) was calculated as weight (kg)/height (m^2).

The SPSS 20.0 program was used for the data analyses. Data were expressed as mean with standard deviation, while Pearson's correlation analysis was used to assess the correlation between UCa/Cr ratio and 24-h urinary calcium excretion. Receiver operator characteristic (ROC) curves were constructed to establish the most appropriate cut-off values of UCa/Cr ratio that would be

CONTACT Gengru Jiang xinhuakidney@163.com

Table 1. Demographic and laboratory data.

	Controls	Patients	P Value
Male sex (%, n)	73.3, 88	80.3, 97	0.167
Age (years)	51.6 (10.7)	52.8 (9.5)	0.358
BMI (kg/m^2)	23.5 (3.0)	23.8 (3.1)	0.406
UCa/Cr(μmol/μmol)	0.15 (0.7)	0.28 (0.11)	<0.001
UAbl/Cr(μmol/μmol)	16.7 (5.8)	40.4 (23.6)	<0.001
Urine pH	6.0 (1.0)	5.8 (0.9)	0.188
Urine density (mg/mL)	1.016 (0.004)	1.015 (0.005)	0.401
24hr urinary calcium excretion (mg)	188 (54)	318 (37)	<0.001
Serum urea mmol/L)	4.3 (0.8)	4.2 (0.8)	0.379
Serum creatinine(μmol/L)	66 (11)	64 (13)	0.110
Serum calcium (mmol/L)	2.32 (0.08)	2.41 (0.83)	<0.001
Serum potassium (mmol/L)	4.0 (0.4)	4.0 (0.4)	0.824
Serum sodium (mmol/L)	140 (3)	140 (3)	0.636
Serum chloride (mmol/L)	106 (4)	106 (4)	0.546

Data mean (SD) or %, n (number of subjects).

indicative of a high probability of calcium nephrolithiasis. Multivariate linear regression analysis was performed to determine whether any of sex, age, BMI, Ualb/Cr, urine pH or density could influence the UCa/Cr ratio. *P* value < 0.05 was considered to be significant.

The characteristics of the participants involved in our study was shown in Table 1. There was no significant difference in age, gender, BMI, urine PH, urine density, serum urea, creatinine and electrolytes in both groups, the value of UCa/Cr ratio in nephrolithiasis patients was higher than healthy volunteers. We also found 24-h urinary calcium excretion, serum calcium and Ualb/Cr were increased in calcium nephrolithiasis patients as compared to healthy volunteers ($p < 0.001$).

The correlation between fasting UCa/Cr ratio and 24-h urinary calcium excretion was highly significant (Figure 1a). We also found positive correlations between UCa/Cr ratio and 24-h urinary calcium excretion in both groups, being 0.70 ($p < 0.001$) in healthy volunteers and 0.76 ($p < 0.001$) in calcium nephrolithiasis patients.

The ROC curve showed the most appropriate cut-off value of fasting UCa/Cr ratio for the estimation of calcium nephrolithiasis was 0.175 μmol/μmol (sensitivity 85.5%; specificity 71.7%; area under the curve 0.862; 95% CI 0.82–0.91; $p < 0.001$, Figure 1b). Multivariate linear regression analysis showed that 24-h urinary calcium excretion ($p < 0.001$), serum calcium ($p < 0.001$) and gender ($p = 0.002$) influenced the UCa/Cr ratio. Age ($p = 0.710$), BMI ($p = 0.252$), Ualb/Cr ($p = 0.817$), urine pH ($p = 0.498$) and urine density ($p = 0.162$) were unrelated to the UCa/Cr ratio.

The present study reported the value of fasting UCa/Cr ratio in normal adults and calcium nephrolithiasis patients, 24-h urinary calcium excretion and serum calcium were the influencing factors of UCa/Cr ratio. Our finding that this ratio has correlates with 24-h urinary calcium excretion suggests that it may be used as a predictive index of calcium nephrolithiasis. We emphasise that the subjects involved in this study were free of several factors (e.g. treated with bisphosphonates, calcium, vitamin D, steroids and diuretics) that may influence the UCa/Cr ratio. Although it has been reported that calciuria measured in a fasting second morning void sample is more representative than the 24-h urine collection, we decided to use the first morning void sample, because it has been widely accepted in the literature.[7,8]

Several studies show mixed results of UCa/Cr ratio in different adult populations.[4,9,10] For example, we found the value of UCa/Cr ratio in calcium nephrolithiasis patients to be higher than those reported by Arrabal

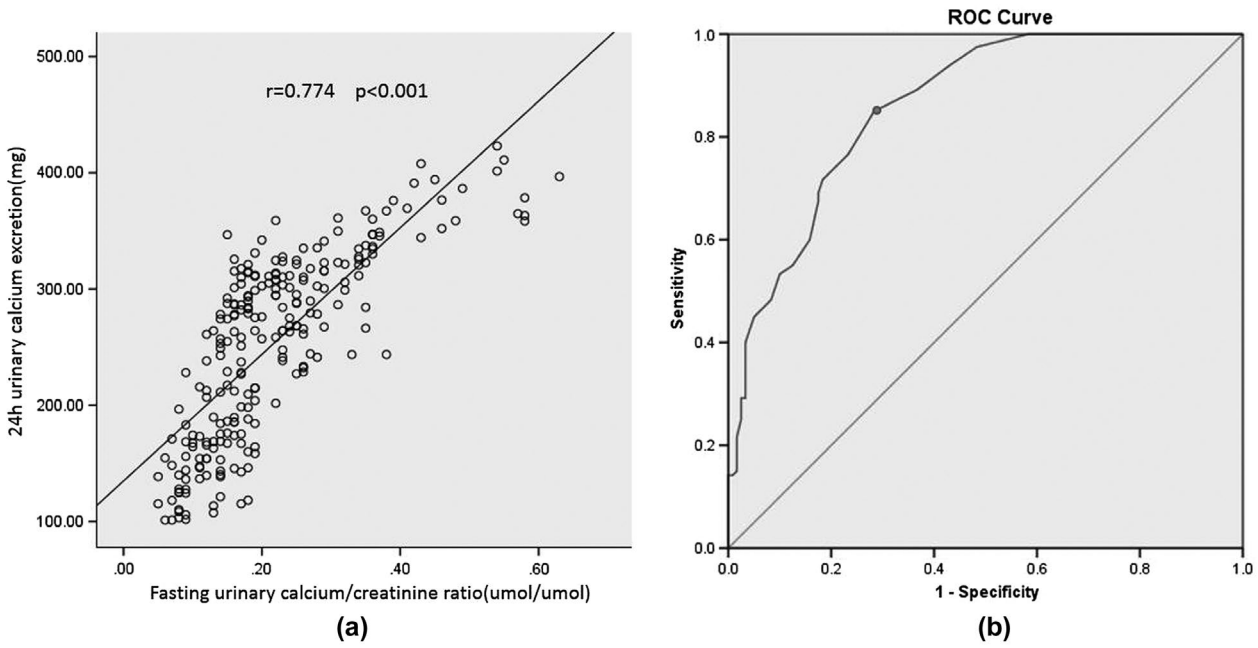

Figure 1. (a). Pearson correlation between fasting urinary calcium/creatinine (UCa/Cr) ratio and 24-h urinary calcium excretion. (b). Receiver operating characteristic (ROC) curve analysis of fasting urinary calcium/creatinine (UCa/Cr) ratio. The cut-off value of UCa/Cr ratio (marked with a black dot on the curve) was defined as 0.175 umol/umol (sensitivity, 85.5%; specificity, 71.7%; area under the curve, 0.862; $p < 0.001$).

et al. [11]. This, and other differences, may be due to nutrition, age, sex, comorbidity, race and other factors which should be taken into consideration.

The correlation between UCa/Cr ratio and 24-h urinary calcium excretion is controversial. Gokce et al. observed a very strong correlation between Ca/Cr ratio in single-voided urine samples and 24-h total calcium excretion in adults.[12] Other studies showed a strong and positive correlation between the UCa/Cr ratio and 24-h urinary calcium excretion in calcium lithiasis patients.[13] We obtained the same results that the correlation between the UCa/Cr ratio and 24-h urinary calcium excretion was positive in both normal adults and calcium nephrolithiasis patients. Despite this agreement, some studies showed no convincing correlation, while one reported that the early morning spot urine cannot replace the 24-h urine collection in the evaluation of urinary metabolic abnormalities in those who form a renal stone.[14]

There are limitations in our study. First, we did not measure the UCa/Cr ratio on double urine samples, it is possible that samples collected at different times would exhibit different results. Next, was the lack of biochemical parameters that would allow for a full characterisation of calcium metabolism and acid-base status: we have no data on PTH, vitamin D or bicarbonate. However, we believe our study has adequate power to support our conclusions.

In conclusion, we recommend that calcium nephrolithiasis patients take a fasting UCa/Cr ratio test, because it is cheaper and simpler than the 24-h urine test and has demonstrated a comparable performance. Our data indicates that the most appropriate cut-off value for the prediction of calcium nephrolithiasis is 0.175 µmol/µmol. This work represents an advance in biomedical science because it shows fasting UCa/Cr ratio could be a predictive index of calcium nephrolithiasis and very simple and convenient for clinical use.

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Disclosure statement

The authors declare that they have no conflict of interest.

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