Original Paper

Epidemiologic Association of Nonalcoholic Fatty Liver Disease and Urinary Calculi

A Population-based Cross-sectional Study in Southern China

Yan-ping Wei,[1] Xing-gu Lin,[1] Rong-quan He,[1] Juan Shen,[1] Si-long Sun,[1] Gang Chen,[1,2] Qiu-yan Wang,[1] Jian-feng Xu,[1] Zeng-nan Mo[1,3,4,5,6]

[1]Center for Genomic and Personalized Medicine, Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, China
[2]Department of Pathology, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, China
[3]Institute of Urology and Nephrology, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, China
[4]Guangxi Key Laboratory for Genomic and Personalized Medicine, Nanning, Guangxi Zhuang Autonomous Region, China
[5]Guangxi Collaborative Innovation Center for Genomic and Personalized Medicine, Nanning, Guangxi Zhuang Autonomous Region, China
[6]Guangxi Key Laboratory of Colleges and Universities, Nanning, Guangxi Zhuang Autonomous Region, China

Keywords. nonalcoholic fatty liver disease, urinary calculus, China

Introduction. Nonalcoholic fatty liver disease (NAFLD) has been reported to have effects on kidney diseases; however, a link between NAFLD and urinary calculi remains to be confirmed. This study was conducted on a male population based on our previous Fangchenggang Area Male Health and Examination Survey in Guangxi, China in order to estimate the frequency of urinary calculi and assess the association between NAFLD and urinary calculi while controlling for possible confounders.

Materials and Methods. This was a population-based cross-sectional study conducted in the Fangchenggang region in Guangxi, China. The diagnoses of NAFLD and urinary calculi were made by ultrasonography. Clinical and laboratory findings were analyzed to investigate whether NAFLD was a risk factor for urinary calculi.

Results. A total of 3719 men were enrolled (age range, 17 to 88 years). Slightly more than a quarter (26.5%) of the participants were diagnosed with NAFLD. The percentage of urinary calculi in all participants was 6.9%, and the percentage of NAFLD patients with urinary calculi (8.4%) was significantly higher than that among patients without NAFLD (6.4%, $P < .05$). Advanced age; high body mass index; elevated levels of blood glucose, cholesterol, triglycerides, and low-density lipoprotein cholesterol; low education; lower or higher physical activity; and NAFLD were independent risk factors for urinary calculi ($P < .05$).

Conclusions. Our results showed that NAFLD was associated with a higher incidence of urinary calculi in this cohort and NAFLD might represent a risk factor for urinary calculi.

IJKD 2018;12:112-9
www.ijkd.org

INTRODUCTION

The incidence of nephrolithiasis, a common kidney disease, has increased significantly in the past 2 decades. About 5% of adults were reported to experience urinary calculi from 1988 to 1994 in the United States by the National Health and Nutrition Examination Survey III, and this frequency represented a 4% increase compared to that in the phase II of that study conducted from 1976 to 1980.[1] The most recent studies showed that the incidence of nephrolithiasis among Americans is 9.4% to 11.9% for men and 7% for women.[2] The incidence of urinary calculi in European countries varies from 4.7% to 10%. In Germany, the incidence was 1.47%, which represented a 3-fold increase over the past 20 years.[3,4] In Britain, a 63% increase in the incidence of nephrolithiasis episodes and a 127% increase in ureteroscopic calculus treatments were recorded in the last decade.[5] The incidence of urinary calculi also varies in Asian countries. About 9.01% of men and 5.79% of women were diagnosed with upper tract urolithiasis in Taiwan based on the National Health Insurance Research Database containing 22.72 million enrollees.[6] Ahmad and colleagues[7] reported a urinary calculus incidence of 19.1% among the examined participants, and the prevalence of urinary calculi according to country of origin in ascending order of frequency was 7.4% in Saudi Arabia, 15.4% in Eritrea, 16.2% in Bangladesh, 17.6% in Sudan, 20.5% in Yemen, 23.3% in India, 24.9% in Pakistan, and 29.5% in Egypt. Approximately, 75% of the calculi were located within the kidney.

The incidence of urolithiasis is increasing worldwide. Epidemiological, biochemical, and genetic factors including aging, eating habits, greenhouse effect, and advanced diagnostic tools are associated with this increase.[8] An increasing incidence of nephrolithiasis not only brings patients excruciating discomfort and complications, but also higher medical expenses to societies.[9]

Urinary calculi are formed by precipitating calculi in the urological system and are facilitated by reduced solubility of salts in the urinary tract. Urinary calculi likely occur when urine is "supersaturated" with insoluble compounds such as calcium oxalate and phosphate, which may result from ongoing overdehydration or a genetic predisposition to overexcrete these ions into the urine.[10] Socioeconomically, like metabolic syndrome, urinary calculi are also perceived as an affluence-associated disease as it is more prevalent in wealthy countries.[11,12] Mechanistically, metabolic diseases like metabolic syndrome can alter urinary constituents, facilitating accumulation of both uric acid and calcium oxalate calculi.

Nonalcoholic fatty liver disease (NAFLD) is an increasingly alarming healthy issue in the 21st century.[13,14] The estimated prevalence of NAFLD ranges from 6% to 35% worldwide, affecting an average 20% of the general population.[15] As many as 15% to 20% of Chinese adults may have been affected, and the incidence continues to surge as a result of the increasing frequency of overweight and obesity in the Chinese population.[16]

Accumulating evidence indicates that the increasing incidence of chronic kidney disease may be associated with the increased NAFLD incidence,[17] implying that NAFLD may represent a newly uncovered risk factor for chronic kidney disease. Furthermore, NAFLD and chronic kidney disease may share some vital cardiometabolic risk factors and possible mutual pathophysiological mechanisms.[18] However, a possible link between NAFLD and urinary calculi has not been well established. A literature search of the MEDLINE database only found 3 recent studies that suggested an association between fatty liver and renal calculus disease. Einollahi and coworkers[19] investigated the link between NAFLD and the incidence of urinary calculi. For the first time, Paz and colleagues[20] showed a significantly higher percentage of fatty liver disease among the group of patients with urinary calculi using computed tomography as the imaging diagnostic modality, supporting the notion of association between urinary calculi and fatty liver, especially in the male population. Although pioneering, their research did not account for confounding factors such as age, education status, smoking status, alcohol drinking, physical activity, and body mass index (BMI). To verify the suggested link between NAFLD and urinary calculi, we conducted this population-based cross-sectional study using the database of the Fangchenggang Area Male Health and Examination Survey (FAMHES) in Guangxi, China.

MATERIALS AND METHODS

Study Population

In 2009, the FAMHES was conducted in the Medical Centre of Fangchenggang First People's Hospital to investigate the impact of environmental and genetic factors on the development of chronic diseases. After obtaining the informed consent from all participants and the approval of the local ethics committee, data from physical examination of 4303 male participants were collected.

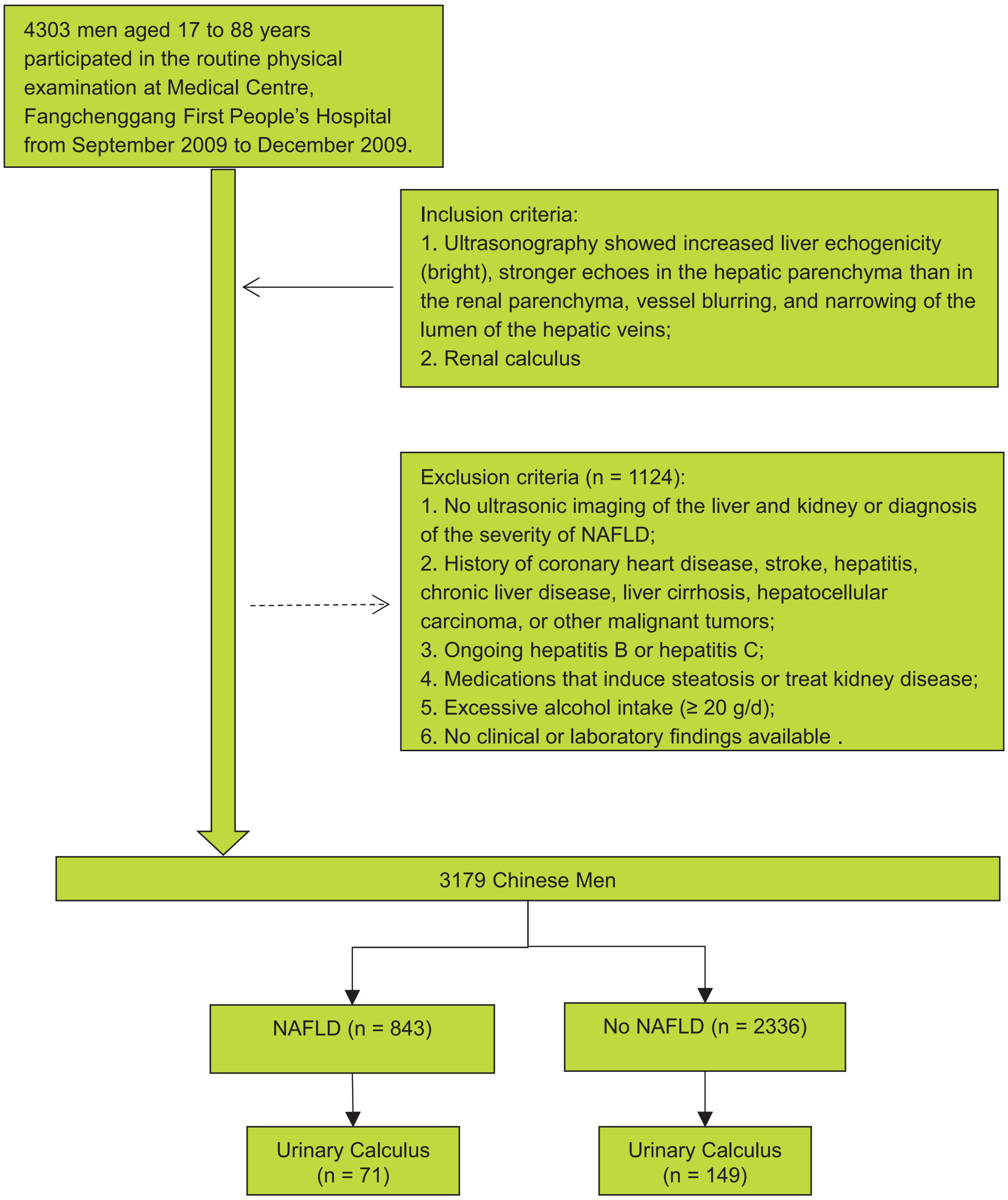
Participants in the FAMHES were excluded if one of following conditions was present: no ultrasonic imaging of the liver and kidney or diagnosis of the severity of NAFLD available; a history of coronary heart disease, stroke, hepatitis, hepatocellular carcinoma, or other malignant tumors; ongoing hepatitis B or hepatitis C infection (presence of hepatitis B surface antigen or antibodies to hepatitis C virus) or liver cirrhosis; use of any medications that would induce steatosis or treat kidney disease; high alcohol consumption defined by the NAFLD diagnosis[21,22]; and unavailability of clinical or laboratory findings. In total, 3179 Chinese male participants were finally selected from the FAMHES for this study, and their age ranged from 17 to 88 years (Figure).

Diagnosis of Nonalcoholic Fatty Liver Disease

All of the participants were subjected to abdominal ultrasonographic examination, which was performed by 2 experienced roentgenologists using a 5.0-MHz transducer. Data on hepatic size, morphology, and echoic pattern were collected for each participant. The severity of the fatty liver was categorized as mild, moderate, or severe.[23-31]

Urinary Calculus Diagnosis

The diagnosis of urinary calculi was established by ultrasonographic imaging, as it is a routine method for the detection of urinary calculi.[32] In this study, any calculus that was greater than 3 mm in diameter was detected by our 2 experienced radiologists. Patients with calculi in the kidneys, ureters, or both were enrolled, and those with bladder calculi were excluded.



The flow chart of selecting participants. NAFLD indicates nonalcoholic fatty liver disease.

Epidemiological Survey

A standardized questionnaire was used to collect information on baseline demographic characteristics (such as age, height, weight, family, education, and occupation), social habits (cigarette smoke, amount of alcohol, and body kinematics), health status, previous medical treatment, and medication history.[33] All data were managed using the EpiData 3.1 software. Body mass index was calculated as weight (in kilograms) divided by body area (in meters squared). Average daily alcohol intake was assessed based on the number of drinks consumed daily, weekly, or monthly, and the volume and concentration of alcohol in the drink.[28,34]

Statistical Analysis

The mean, median, quartile, or percentage values were used to describe the results. The Student *t* test or the chi-square test was selected when appropriate. Logistic regression analysis was used to assess the association of NAFLD quartiles with the presence of urinary calculi. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the occurrence of urinary calculi among the NAFLD patients. *P* values less than .05 were considered significant.

RESULTS

The clinical and laboratory characteristics of the participants are shown in Table 1, and they were

Table 1. Baseline Characteristics of Participants Stratified by Presence or Absence of Urinary Calculi

	Participants		
Characteristic	No Urinary Calculi	Urinary Calculi	*P*
Number of participants	2959	220	…
Age, y	36.00 (29.00 to 45.00)	42.50 (36.00 to 50.00)	< .001
Systolic blood pressure, mm Hg	120.00 (110.00 to 130.00)	120.00 (110.00 to 130.00)	.03
Diastolic blood pressure, mm Hg	80.00 (70.00 to 82.00)	80.00 (70.00 to 86.00)	.06
Body mass index, kg/m^2	23.38 (20.97 to 25.82)	24.07 (21.94 to 26.15)	.001
Urea, mg/dL	31.93 (27.11 to 37.35)	33.13 (27.29 to 39.04)	.06
Creatinine, mg/dL	9.84 (8.93 to 10.74)	10.00 (8.82 to 11.17)	.10
Uric acid, mg/dL	6.34 (5.53 to 7.26)	6.38 (5.59 to 7.64)	.17
Glucose, mg/dL	93.70 (88.30 to 100.912)	95.51 (88.30 to 102.71)	.03
Cholesterol, mg/dL	217.33 (191.03 to 244.01)	228.15 (199.92 to 254.45)	< .001
Triglyceride, mg/dL	105.26 (70.76 to 169.83)	118.53 (73.42 to 186.64)	.03
High-density lipoprotein cholesterol, mg/dL	51.82 (45.24 to 59.94)	50.66 (44.86 to 58.78)	.35
Low-density lipoprotein cholesterol, mg/dL	113.69 (94.35 to 133.80)	121.04 (100.54 to 143.08)	.001
Glomerular filtration rate, mL/min	112.38 (100.77 to 126.85)	107.27 (94.00 to 122.70)	.001
Education level, years, n (%)			
Up to grade 6	20 (0.68)	6 (2.72)	.001
Grade 7 to 9	548 (18.52)	31 (14.10)	.10
Grade 10 and higher	2391 (80.80)	183 (83.18)	.39
Smoking status, n (%)			
Nonsmoker	1408 (47.58)	97 (44.09)	.32
Quitter	1401 (47.35)	106 (48.18)	.81
Current smoker	150 (5.07)	17 (7.73)	.09
Drinking status, n (%)			
Nondrinker	402 (13.58)	24 (10.91)	.26
Quitter	2435 (82.30)	186 (84.54)	.40
Current drinker	122 (4.12)	10 (4.55)	.76
Physical activity, n (%)			
Low	2167 (73.23)	140 (63.64)	.002
Moderate	390 (13.18)	26 (11.82)	.56
High	402 (13.59)	54 (24.54)	< .001
Nonalcoholic fatty liver disease, n (%)			
No	2187 (73.91)	149 (67.73)	.045
Mild	462 (15.61)	30 (13.64)	.43
Moderate	240 (8.11)	27 (12.27)	.03
Severe	70 (2.37)	14 (6.36)	< .001

grouped based on the presence or absence of urinary calculi. Among the 3179 participants included, 2187 (68.8%) were healthy without NAFLD or urinary calculi. Among the remaining participants, 843 (26.5%, mean age, 40.90 years; age range, 20 to 88 years) were diagnosed with NAFLD and 220 with urinary calculi (mean age, 43.59 years; age range, 20 to 81 years). Urinary calculi were detected in 6.4% of the participants without NAFLD and in 8.4% of those with NAFLD ($P < .05$; OR, 1.35; 95% CI, 1.01 to 1.81). Advanced age; high BMI; elevated levels of blood glucose, cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDLC); low education; lower or higher physical activity; and NAFLD were risk factors for urinary calculi ($P < .05$).

The rates of recurrent urinary calculi in our study were 3.5%, 5.0%, and 3.0% for the total cohort, the NAFLD group, and the non-NAFLD group, respectively ($P < .05$).

There was a noticeable increase in the OR for urinary calculi with increasing severity of NAFLD, from 0.953 in the participants without NAFLD to 2.936 in those with severe NAFLD in the nonadjusted model (model 1, $P = .001$). The same effect was detected in the calibrated age-adjusted model (model 2, $P = .006$), the model further adjusted for education status, smoking habit, alcohol consumption, and physical activity (model 3, $P = .01$), and the model further adjusted for BMI (model 4, $P = .047$). After excluding many factors including age, education status, smoking, alcohol consumption, physical activity, and BMI, participants with severe NAFLD still had a 2.11-fold greater risk of urinary calculi (Table 2).

DISCUSSION

In this study, we investigated the frequencies of both NAFLD and urinary calculi in a cohort consisting of 3179 men who participated in an annual physical examination. We found that 26% of participants had NAFLD and 6.9% of them carried urinary calculi. The incidence of urinary calculi in participants with NAFLD was significantly higher than that in participants without NAFLD. In addition, the frequency of recurrent urinary calculi in the NAFLD group (5.0%) was higher than that in the non-NAFLD group (3.0%). Our correlation analysis showed that NAFLD was one of the risk factors for developing urinary calculi and the recurrence rate of urinary calculi is regarded as one of the risk factors for fatty liver. Nonalcoholic fatty liver disease remained a risk factor that increased the likelihood of developing a urinary calculus by 2.1-fold after adjustment for the impact of other risk factors in our analysis. Interestingly, the OR for urinary calculi increased consistently from 0.953 in participants without NAFLD to 2.936 in those with severe NAFLD. Our results confirmed the epidemiologic link between NAFLD and urinary calculi suggested by early reports.[19,20,35]

Despite our confirmation that NAFLD is a newly uncovered risk factor for urinary calculi, we cannot yet offer a clear explanation of why NAFLD could increase the risk for urinary calculi. It is conceivable that NAFLD may mechanistically facilitate calculus formation in the renal system. Fundamentally, NAFLD is a metabolic disease, which may cause the production of altered metabolites that could change the composition as well as concentrations of metabolites in the urine flow, leading to accelerated accumulation and precipitation of calcium and other salts.

In addition, NAFLD is often associated with overweight or obesity. Recent retrospective and cross-sectional studies revealed that metabolic syndrome and a greater BMI were independent risk factors for nephrolithiasis.[36-39] Additionally,

Table 2. Multivariable Analysis for Nonalcoholic Fatty Liver Disease and Urinary Calculi among Participants Grouped by Ascending Severity of Nonalcoholic Fatty Liver Disease*

Model	Degree of NFLD				*P* for Trend
	Absent (n = 2336)	Mild (n = 492)	Moderate (n = 267)	Severe (n = 84)	
Model 1	1.000	0.953 (0.636 to 1.429)	1.651 (1.073 to 2.541)	2.936 (1.615 to 5.335)	.001
Model 2	1.000	0.913 (0.608 to 1.371)	1.499 (0.970 to 2.314)	2.545 (1.393 to 4.649)	.006
Model 3	1.000	0.841 (0.558 to 1.268)	1.392 (0.897 to 2.160)	2.435 (1.318 to 4.501)	.01
Model 4	1.000	0.782 (0.507 to 1.207)	1.234 (0.750 to 2.028)	2.114 (1.079 to 4.141)	.047

*Model 1 was not adjusted for any variable; model 2 was adjusted for age; model 3 was further adjusted for education status, smoking, alcohol consumption, and physical activity; and model 4 was further adjusted for body mass index.

these studies also suggested that insulin resistance, a hallmark of metabolic syndrome, contributes to uric acid nephrolithiasis. These studies support the potential role of insulin resistance in an impaired urinary synthesis of ammonia could lead to decreased urinary ammonia excretion and low urinary pH. Ultimately, it may lead to the formation of uric acid calculi.[39-41] Insulin resistance, which occurs in association with obesity, can also alter the composition of the urine. Urinary composition in the obese population seems to contain higher levels of metabolites or wastes known to be lithogenic compared with the nonobese population.[42] Unduly acidic urine (urine pH $\leq$ 5.5) leads to precipitation of the sparingly soluble protonated uric acid, increasing the predisposition to uric acid nephrolithiasis.[43] Indeed, studies of 3 large groups of individuals with nephrolithiasis have demonstrated that higher weight is associated with lower urinary pH.[42,44] Although a lower urinary pH is generally associated with uric acid calculi, an impaired ability to excrete acid could result in hypocitraturia, an important risk factor for calcium calculi.

In addition, it can also indirectly contribute to the retention and precipitation of salts in the renal tract because individuals with overweight and obesity are inclined to be less active, which can lead to a reduced flow rate in the renal system that could favor the precipitation of salts. Indeed, we found in this study that both high BMI and reduced physical activity represented additional risk factors for urinary calculi.

Imaging techniques, including ultrasonography, computed tomography, and magnetic resonance imaging, offer reliable diagnosis of NAFLD. A recent meta-analysis showed that ultrasonography is accurate at detecting moderate to severe fatty liver, with a specificity reaching 93.4% and sensitivity of 84.8% for NAFLD diagnosis.[45] The diagnosis of urinary calculi with the ultrasonography is also appropriate and cost effective for this cohort that involved more than 3000 participants. We are confident about both the NAFLD and urinary calculus diagnoses in this study.

Although NAFLD primarily affects the liver, it is a systematic disease involving multiple organs. An implication of our results that confirmed the association between NAFLD and urinary calculi is that an increase in the prevalence of NAFLD may lead to an increase in the incidence of urinary calculi. An effective management of NAFLD should focus on the prevention and mitigation of damage to multiple organs.

Although we fulfilled the purpose of this cross-sectional study and verified the suggested link between NAFLD and urinary calculi, there are a few limitations. One is that our study did not include women and the findings from the male-only population may not be representative for the general population. In addition, this study was conducted in a single center and our findings need to be further verified in multicenter large population-based prospective studies.

CONCLUSIONS

We confirmed that the incidence of urinary calculi was significantly higher in participants with NAFLD than those without NAFLD. Our further analysis showed that NAFLD increases the risk for urinary calculi by 2.1-fold after removal of confounding factors. Our results suggest a possible link in the pathogenic processes of NAFLD and urinary calculus disease.

ACKNOWLEDGMENTS

We thank the staff of Fangchenggang First People's Hospital, Fangchenggang, China, for their contribution to this investigation. Thanks are due to support from Guangxi Natural Science Fund for Innovation Research Team (2013GXNSFFA019002) and the National Natural Science Foundation of China (grants number, 81370857).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Stamatelou KK, Francis ME, Jones CA, Nyberg LM,Curhan GC. Time trends inreported prevalence of kidney calculi in the United States: 1976–1994. KidneyInt. 2003;63:1817-23.
2. Charles D. Scales Jr, Alexandria C. Smith, Janet M. Hanleyb CSS. Prevalence of Urinary Calculi in the United States Charles. Eur J Urol. 2012;62:160-5.
3. Romero V, Akpinar H, Assimos DG. Kidney calculi: a global picture ofprevalence,incidence, and associated risk factors. Rev Urol. 2010;12:e86-96.
4. Hesse A, Brandle E, Wilbert D, Kohrmann KU, Alken P. Study on the prevalence andincidence of urolithiasis in Germany comparing the years 1979 vs. 2000. Eur Urol. 2003;44:709-13.

5. Turney BW, Reynard JM, Noble JG, Keoghane SR. Trends in urological calculus disease. BJU Int. 2012;109:1082-7.
6. Huang WY, Chen YF, Carter S, Chang HC, Lan CF, Huang KH. Epidemiology of upper urinary tract calculus disease in a Taiwanese population: a nationwide, population based study. J Urol. 2013;189:2158-63.
7. Ahmad F, Nada MO, Farid A Bin, Haleem MA, Razack SMA. Epidemiology of urolithiasis with emphasis on ultrasound detection: a retrospective analysis of 5371 cases in Saudi Arabia. Saudi J Kidney Dis Transplant. 2015;26:386-91.
8. Alatab S, Pourmand G, El Howairis Mel F, et al. National profiles of urinary calculi: a comparison between developing and developed worlds. Iran J Kidney Dis. 2016;10:51-61.
9. Safarinejad MR. Adult urolithiasis in a population-based study in Iran: Prevalence, incidence, and associated risk factors. Urol Res. 2007;35:73-82.
10. Han H, Segal AM, Seifter JL, Dwyer JT. Nutritional Management of Urinary Calculi (Nephrolithiasis). Clin Nutr Res. 2015;4:137-52.
11. Stapleton AE, Dziura J, Hooton TM, et al. Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: A randomized controlled trial. Mayo Clin Proc. 2012;87:143-50.
12. Marchini GS, Sarkissian C, Tian D, Gebreselassie S, Monga M. Gout, calculus composition and urinary calculus risk: A matched case comparative study. J Urol. 2013;189:1334-9.
13. Koppe SWP. Obesity and the liver: Nonalcoholic fatty liver disease. Transl Res. 2014;164:312-22.
14. Yuan L, Bambha K. Bile acid receptors and nonalcoholic fatty liver disease. World J Hepatol. 2015;7:2811-8.
15. Vernon G, Baranova A, Younossi ZM. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274-85.
16. Fan JG. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. J Gastroenterol Hepatol. 2013;28:11-7.
17. Targher G, Mantovani A, Pichiri I, et al. Nonalcoholic fatty liver disease is independently associated with an increased incidence of chronic kidney disease in patients with type 1 diabetes. Diabetes Care. 2014;37:1729-36.
18. Orlić L, Mikolasevic I, Bagic Z, Racki S, Stimac D, Milic S. Chronic Kidney Disease and Nonalcoholic Fatty Liver Disease—Is There a Link? Gastroenterol Res Pract. 2014;2014:847539.
19. Einollahi B, Naghii MR, Sepandi M. Association of nonalcoholic fatty liver disease (NAFLD) with urolithiasis. Endocr Regul. 2013;47:27-32.
20. Paz D, Guralnik L, Haifa IL, Nesher IL. Association of renal calculus (urolithiasis)with nonalcoholic fatty liver (NAFL). Eur Soc Radiol.2015;ECR 2015:c-2056.
21. Liu JJ, Chen YY, Mo ZN, et al. Relationship between serum osteocalcin levels and non-alcoholic fatty liver disease in adult males, South China. Int J Mol Sci. 2013;14:19782-91.
22. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: Summary of an AASLD Single Topic Conference. Hepatology. 2003;37:1202-19.
23. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002;123:745-50.
24. Huh JH, Ahn SV, Koh SB, et al. A prospective study of fatty liver index and incident hypertension: The KoGES-ARIRANG study. PLoS One. 2015;10:1-13.
25. Huh JH, Lee KJ, Lim JS, et al. High dietary sodium intake assessed by estimated 24-h urinary sodium excretion is associated with NAFLD and hepatic fibrosis. PLoS One. 2015;10:1-11.
26. Hossain IA, Akter S, Rahman MK, Ali L. Gender specific association of serum leptin and insulinemic indices with nonalcoholic fatty liver disease in prediabetic subjects. PLoS One. 2015;10:1-12.
27. Kim G, Lee YH, Park YM, et al. Use of a Diabetes Self-Assessment Score to Predict Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Medicine (Baltimore). 2015;94:e1103.
28. Ahmed M. Non-alcoholic fatty liver disease in 2015. World J Hepatol. 2015;7:1450-9.
29. Wei Y, Tian Q, Zhao X, Wang X. Serum transforming growth factor beta 3 predicts future development of nonalcoholic fatty liver disease. Int J Clin Exp Med. 2015;8:4545-50.
30. Chung GE, Choi S-Y, Kim D, et al. Nonalcoholic fatty liver disease as a risk factor of arterial stiffness measured by the cardioankle vascular index. Medicine (Baltimore). 2015;94:e654.
31. Cengiz M, Sentürk S, Cetin B, Hasanefendioğlu A, Bayrak SUB. Sonographic assessment of fatty liver:interobserver and intraobserver variability. Int J Clin Exp Med. 2014;7:5453-60.
32. Türk C, Petřík A, Sarica K, et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. Eur Urol. 2016;69:468-74.
33. Tan A, Gao Y, Yang X, et al. Low serum osteocalcin level is a potential marker for metabolic syndrome: Results from a Chinese male population survey. Metabolism. 2011;60:1186-92.
34. Youming L. Guidelines for management of nonalcoholic fatty liver disease: An updated and revised edition. Chin J Hepatol. 2010;18:163-6.
35. Nam IC. Association of non-alcoholic fatty liver disease with renal calculus disease detected on computed tomography. Eur J Radiol Open. 2016;3:195-9.
36. Sakhaee K. Recent advances in the pathophysiology of nephrolithiasis. Kidney Int. 2009;75:585-95.
37. Ramaswamy K, Shah O. Metabolic syndrome and nephrolithiasis. Transl Androl Urol. 2014;3:285-95.
38. Taylor EN, Stampfer MJ, Curhan GC. Obesity, Weight Gain, and the Risk of Urinary Calculi. JAMA. 2005;293:455-62.
39. Sakhaee K, Adams-Huet B, Moe OW, Pak CY .Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int. 2002;62:971-9.

40. Abate N, Chandalia M, Cabo-Chan Jr AV, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. Kidney Int. 2004;65:386-92.
41. Li H, Klett DE, Littleton R, Elder JS, Sammon JD. Role of insulin resistance in uric acid nephrolithiasis.World J Nephrol. 2014;3:237-42.
42. Powell CR, Stoller ML, Schwartz BF, et al. Impact of body weight on urinary electrolytes in urinary calculus formers. Urology. 2000;55:825-30.
43. Sakhaee K, Maalouf NM. Metabolic Syndrome and Uric Acid Nephrolithiasis. Semin Nephrol. 2008;28:174-80.
44. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. Kidney Int. 2004;65:1422-5.
45. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: A meta-analysis. Hepatology. 2011;54:1082-90.

Correspondence to:
Jian-feng Xu, MD
Center for Genomic and Personalized Medicine, Guangxi Medical University, 22 Shuangyong Road, Nanning, Guangxi Zhuang Autonomous Region 530021, China
Tel: +86771 5641040
E-mail: jxu@wakehealth.edu

Zeng-nan Mo, MD
Center for Genomic and Personalized Medicine, Guangxi Medical University, 22 Shuangyong Road, Nanning, Guangxi Zhuang Autonomous Region 530021, China
Tel: +86771 5353342
Fax: +86771 5353342.
E-mail: zengnanmo@hotmail.com

Yan-ping Wei, Xing-gu Lin, and Rong-quan He contributed equally as first authors, and Jian-feng Xu and Zeng-nan Mo contributed equally as corresponding authors.

Received May 2017
Revised December 2017
Accepted December 2017