



## Association of non-alcoholic fatty liver disease with renal stone disease detected on computed tomography

In Chul Nam (MD)<sup>a</sup>, Jung Hee Yoon (MD)<sup>a,\*</sup>, Seung Ha Park (MD)<sup>b</sup>, JiHwa Ryu (MD)<sup>a</sup>, Seung Ho Kim (MD)<sup>a</sup>, Yedaun Lee (MD)<sup>a</sup>

<sup>a</sup> Department of Radiology, Inje University College of Medicine, Haeundae Paik Hospital, Haeundae-ro 875, Haeundae-gu, Busan 612-030, Korea

<sup>b</sup> Department of Internal Medicine, Inje University College of Medicine, Haeundae Paik Hospital, Haeundae-ro 875, Haeundae-gu, Busan 612-030, Korea

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### ABSTRACT

**Objective:** To evaluate the association between Non-alcoholic fatty liver disease (NAFLD) with renal stone disease detected on computed tomography (CT).

**Method:** A total 1812 patients who underwent abdomen-pelvis CT in July 2015 were included in this study. The inclusion criteria for NAFLD were as follows: (i) lower average Hounsfield unit (HU) of hepatic right lobe, left medial and lateral segment when compared with that of spleen, (ii) patients who having urolithiasis in kidneys, ureters and urinary bladder, and (iii) patients underwent abdomen-pelvis CT including noncontrast image. The statistical significance of the association between NAFLD and renal stone disease was assessed using Chi Square Test. The Odds ratios and 95% CI were calculated to assess the propensity of renal stones disease for NAFLD by using Logistic Regression analysis.

**Results:** The frequency of renal stone disease in patients with NAFLD was higher approximately 19% than those who having renal stone disease without NAFLD. In addition, the presence of NAFLD was linked with renal stone disease showing that detection rate of renal stone disease in patients with NAFLD was markedly high (odds ratio: 5, 95% CI, 3–8.2) ( $p < 0.05$ ) in multivariate analysis.

**Conclusion:** The presence of significant association between NAFLD with renal stone disease and NAFLD may be considered to be an independent variable as a risk factor for renal stone disease.

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### 1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has been recognized as a liver manifestation of the metabolic syndrome [1]. The prevalence of NAFLD from United States, Europe and Asia is reported to be up to third of the human population [2,3]. NAFLD is defined as the presence of at least 5% of the fat component in the liver without any other liver disease including alcohol related liver disease, chronic viral hepatitis, use of medications resulting in hepatic steatosis such as tamoxifen, herb medication or other chronic liver disease such as autoimmune hepatitis. The guideline for NAFLD (endorsed as American Association for the Study of Liver Disease, American College of Gastroenterology and American Gastroenterological) defines sig-

nificant alcohol use as current or recent alcohol consumption more than 21 drinks per a week in men and 14 drinks per a week in women [4]. NASH is a more progressive type of NAFLD and defined histologically by presence of hepatic cell injury with parenchymal steatosis [4].

Recent studies concluded that NAFLD has no direct association with renal function and mild renal function abnormality may have similar risk factors or disease process [5]. Renal stone disease is a common renal disorder associated with crystal deposition in the renal medulla and urinary tract. It is influenced by both intrinsic and extrinsic factors [6]. Recent epidemiological studies have demonstrated that renal stone disease has an association with obesity, diabetes mellitus, hypertension, and metabolic syndrome [7]. These results reveal that metabolic syndrome can result in changes in process of urine concentration and dilution, causing an increased risk of both uric acid and calcium oxalate stone formations [7]. In the basis of these studies, renal stone disease may be related to the metabolic syndrome and can be a component of the metabolic syndrome.

Recently, we noticed a concomitant diagnosis of both fatty liver and renal stones disease in same patient on the basis of com-

\* Corresponding author at: Department of Radiology, Inje University College of Medicine, Haeundae Paik Hospital, Haeundae-ro 875, Haeundae-gu, Busan 612-030, Korea. Tel.: +82 51 797 0384; fax: +82 51 797 0379.

E-mail addresses: [sky\\_hall@naver.com](mailto:sky_hall@naver.com) (I.C. Nam), [radyljh@hanmail.net](mailto:radyljh@hanmail.net) (J.H. Yoon), [SH.Park@paik.ac.kr](mailto:SH.Park@paik.ac.kr) (S.H. Park), [rjhrad@empas.com](mailto:rjhrad@empas.com) (J. Ryu), [radiresi@gmail.com](mailto:radiresi@gmail.com) (S.H. Kim), [chosai81@gmail.com](mailto:chosai81@gmail.com) (Y. Lee).

**Table 1**  
Total number and gender frequency of fatty liver and renal stone disease.

Gender	Fatty liver	Renal stone disease		Number	$\chi^2$ (p)
		Negative	Positive		
Male	Negative	497 (92.2)	42 (7.8)	539 (100)	55.6 ( $p < 0.05$ )
	Positive	100 (69)	45 (31)	145 (100)	
Female	Negative	541 (91.5)	50 (8.5)	684 (100)	16.8 ( $p < 0.05$ )
	Positive	83 (78.3)	23 (21.7)	591 (100)	
Total	Negative	1038 (91.9)	92 (8.1)	1130 (100)	72 ( $p < 0.05$ )
	Positive	183 (72.9)	68 (27.1)	251 (100)	

puted tomography (CT) finding in routine daily practice. Literature reviews by using Pubmed articles demonstrate only two recent studies were performed and revealed the association between fatty liver and renal stone disease. Therefore, the purpose of our study was to evaluate the prevalence of renal stone disease in the patients with NAFLD by using the CT examination.

## 2. Material and methods

This prospectively collected and retrospectively evaluated study was approved by the institutional review board, and informed consent from patients was waived.

### 2.1. Study population

From July 1, 2015 to July 31, 2015, a total of 1812 patients who visited our institute with performed abdomen-pelvis CT initially eligible. The inclusion criteria for NAFLD group were as follows: (i) lower average Hounsfield unit (HU) of hepatic right lobe, left medial and lateral segment when compared with that of spleen [8,9], (ii) patients having radiopaque stones in the urinary tract including kidneys, ureters or urinary bladder, and (iii) patients underwent abdomen-pelvis CT including noncontrast image. Control group were defined as follows: (i) patients underwent abdomen-pelvis CT including noncontrast image, and (ii) patients whose HU of liver parenchyma showed higher than that of spleen. Exclusion criteria were follows: (i) those who underwent abdomen-pelvis CT without noncontrast image, (ii) those who had suboptimal image quality of CT examination due to beam hardening artifact or respiration artifact, and (iii) those who having other liver disease including viral hepatitis, liver cirrhosis, hepatocellular carcinoma, metastasis from other primary cancer, splenectomy status or abundant alcohol consumption.

Of the 1812 cases, 431 were excluded due to absence of noncontrast image ( $n = 257$ ), viral hepatitis, liver cirrhosis or hepatocellular carcinoma ( $n = 134$ ), splenectomy status ( $n = 12$ ), metastasis from other primary malignancy ( $n = 12$ ), abundant alcohol consumption ( $n = 8$ ) and suboptimal image quality ( $n = 8$ ). Finally, 1381 cases (mean age: 55.8 years; range: 19–91 years; male:female = 684:697) were enrolled in this study. The case accrual process is summarized in Fig. 1.

### 2.2. CT protocols

A 128-detector row CT scanner (Definition AS+, Siemens Healthcare, Forchheim, Germany) was used to perform the abdomen-pelvis CT scan. All patients were in the supine position and were scanned from the lung base to the pubic symphysis. We performed a noncontrast scan. The scanning parameters were as follows: tube voltage, 120 kVp; collimation,  $128 \times 0.6$  mm; rotation speed, 0.5 s; pitch, 0.8; reconstruction thickness, 3 or 5 mm; and no reconstruction interval. Automatic exposure control (caredose 4D, Siemens Healthcare) was activated to decrease the radiation dose,

however, automatic tube potential modulation (careKV, Siemens Healthcare) was not switched on. Sagittal and coronal reformatted images were generated with a thickness of 3 mm.

### 2.3. Image analysis

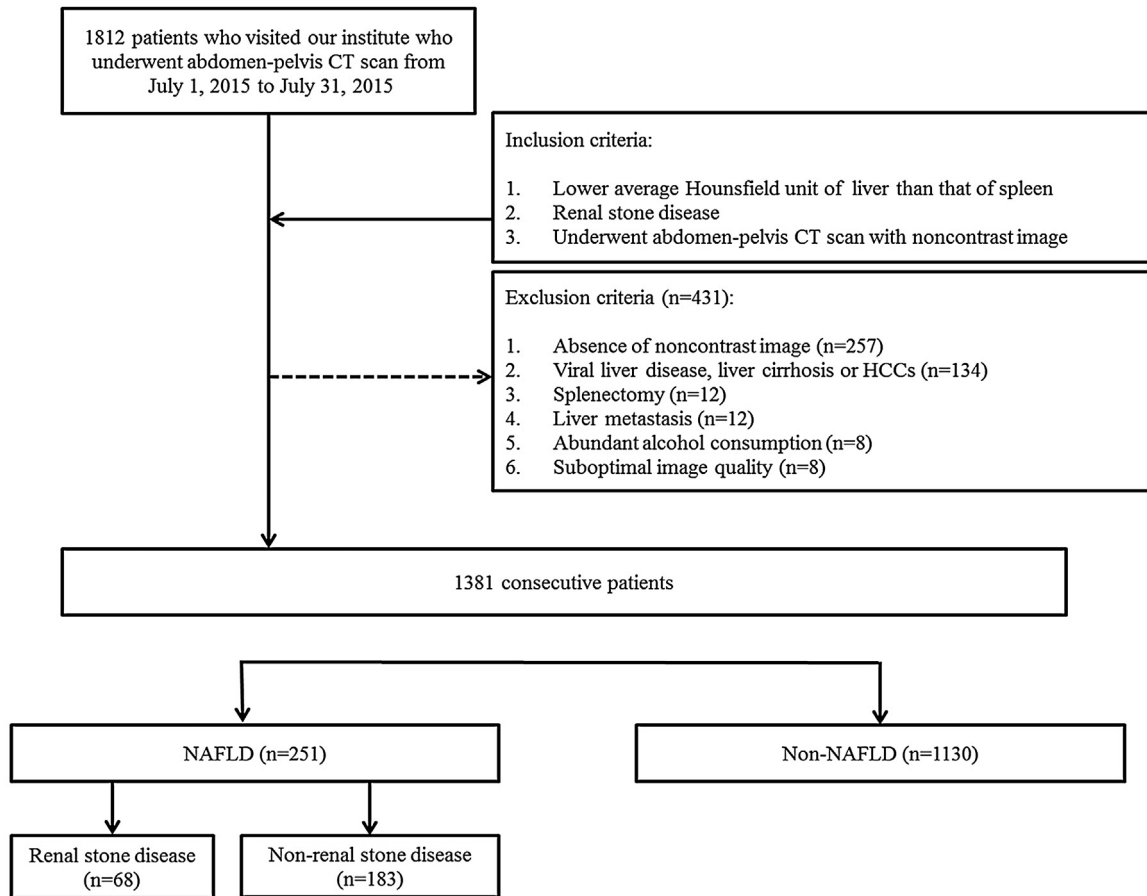
All imaging analysis was performed by a fellowship-complete academic radiologist with 3-year experience in reading abdomen-pelvis CT who was blinded to clinical and laboratory data. To obtain HU of liver parenchyma and spleen, the radiologist derived average HU value of liver parenchyma from three different hepatic segments including right hepatic lobe, left medial and lateral segment by measuring region of interest in each segment. Fatty liver was defined when average HU of liver parenchyma lower than that of spleen [8]. Then 4 weeks later, the radiologist reviewed electronic medical report of all enrolled patients to exclude those who having other liver disease including viral hepatitis, liver cirrhosis, hepatocellular carcinoma, metastasis from other primary cancer, splenectomy status or abundant alcohol consumption (Fig. 2).

### 2.4. Statistical analysis

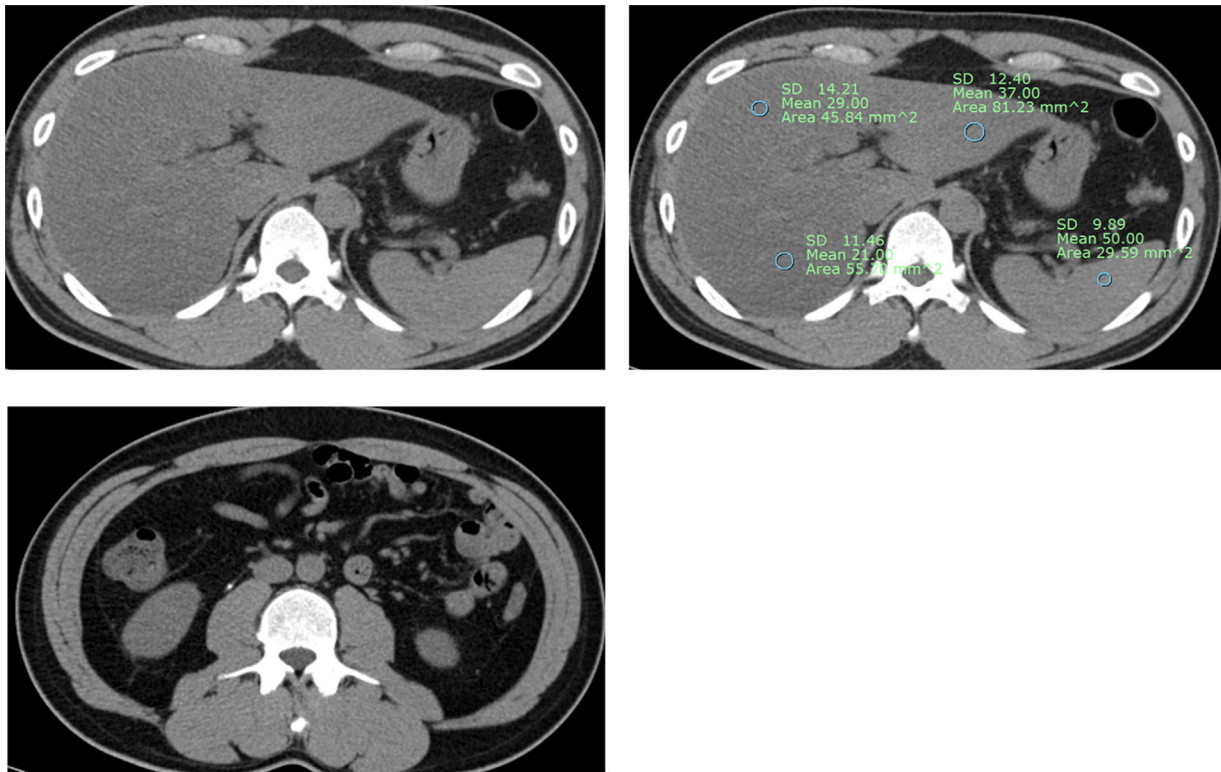
To assess the association between fatty liver and renal stone disease, the Chi Square test was used. The Odds ratios and 95% CI were calculated to assess the propensity of renal stones disease for fatty liver patients by using Logistic Regression analysis. A  $P$  value less than 0.05 was considered to indicate a significant difference. The statistical analysis was performed using Medcalc software for Windows (Medcalc Software Version 11.3.8.0, Mariakerke, Belgium).

## 3. Results

Of the 1381 cases, 1038 were healthy group suggestive of no fatty liver or renal stone disease (75% of total number). Fatty liver were 251 patients (145 men, 106 women; mean age; 54.7 years; age range, 19–90 years) and renal stone disease were 160 patients (87 men, 73 women; mean age, 54.9 years; age range, 20–86 years). The frequency of renal stone disease in fatty liver patient group was 27% ( $n = 68$ ) ( $p < 0.05$ ). In contrast, only 8% was noted as renal stone disease in non-fatty liver patient group ( $n = 183$ ) ( $p < 0.05$ ) (Table 1). The frequency of renal stone disease in male fatty liver patient group was 31% ( $n = 45$ ) and in female fatty liver patients group was 21.7% ( $n = 23$ ) ( $p = 0.208$ ). Diagnosis of fatty liver demonstrated an association with higher risk of developing renal stone disease (odds ratio: 5, 95% CI, 3–8.2) ( $p < 0.05$ ) (Table 2). The mean and standard deviation of HU of liver was  $51.9 \pm 12$  in patient with renal stone disease and fatty liver and  $56.4 \pm 11$  in patient with renal stone disease without fatty liver, respectively ( $p < 0.05$ ). The frequency of fatty liver in renal stone disease ( $n = 160$ ) was 42.5% ( $n = 68$ ), with the frequency of 54.4% and 45.6% in male and female, respectively ( $p = 0.208$ ). In contrast, the frequency of fatty liver in patient without renal stone disease was 15%.



**Fig. 1.** Flowchart of the case accrual process. Computed tomography (CT); Hepatocellular carcinoma (HCC); Non-alcoholic fatty liver disease (NAFLD). NAFLD was defined as fatty liver showing lower Hounsfield Unit than that of spleen on CT.



**Fig. 2.** Noncontrast scan images in a 55-year-old man show diffuse fatty liver and right ureter stone on noncontrast image. He visited our hospital with acute right flank pain, and his laboratory test revealed microscopic hematuria.

**Table 2**  
Multivariate risk factor analysis for renal stone disease.

Dependent variable	Independent variable	Odds ratio	P value
Renal stone disease	Gender	1.127	P=0.491
	Age	0.998	P=0.71
	Hounsfield Unit	1.01	P=0.294
	Fatty liver	4.996	P<0.05

#### 4. Discussion

Our study showed that frequency of renal stone disease in patient with NAFLD was higher approximately 19% than those who having renal stone disease without NAFLD. In addition, the presence of NAFLD was linked with renal stone disease showing that detection frequency of renal stone disease in patients with NAFLD was markedly higher (odds ratio: 5, 95% CI, 3–8.2) ( $p < 0.05$ ) in multivariate analysis. On the basis of these findings, we suggested that there's significant association between NAFLD with renal stone disease and NAFLD may be considered to be an independent variable as a risk factor for stone formation.

Our results correspond well with those of previous studies [10,11]. Einollahi et al. [10] investigated 11245 ultrasonography report in a cross sectional study. They found that the detection rate of renal stone disease was 17% in patients with NAFLD and 8% in patients without NAFLD, respectively. In addition, for NAFLD patients, detection or diagnosis of fatty liver was associated with a higher risk of developing renal stone disease ( $p < 0.0001$ ), (odds ratio: 2.4, 95% CI 2.1–2.7). Even though the detection rate of renal stone disease was significantly higher in patients with NAFLD than that of patients without NAFLD in their study, however, it was lower than that of our study. A discrepancy between our study and theirs could be the difference of diagnostic performance between ultrasonography and CT. Published sensitivity and specificities of CT routinely performed with slice collimations of less than 3 mm approach 98%–100% [12]. Also, a meta-analysis reported a sensitivity of 97% and a specificity of 95% for the detection of obstructive urolithiasis with CT [13]. However, Ray et al. [14] performed a prospective evaluation of renal ultrasonography in the Emergency Department followed by CT examination for the detection of urolithiasis and they revealed that US performed poorly with an accuracy of 67–77% and the limitation of US in clinical practice. Thus, we believe that it might be difficult to properly evaluate urolithiasis by using US resulting in relatively lower detection rate of urolithiasis in patients. Paz et al. [11] retrospectively analyzed a total of 100 patients who were indicated for renal colic and performed noncontrast CT images and they reported 37.5% NAFLD in the positive urinary stone disease group as compared to 10% in the non-urinary stone disease group with statistical significance. Our study revealed that detection rate of NAFLD was 42.6% in positive renal stone disease and 15% in non-renal stone disease. Also, they revealed that detection rate of urolithiasis was 93.8% in NAFLD and 73.5% in non-NAFLD, respectively. Although the detection rate of renal stone disease was significantly higher in patients with NAFLD than that of patients without NAFLD in their study, however, detection rate of urolithiasis was extremely higher than that of our study. A discrepancy between our study and theirs could be the difference of inclusion criteria. All enrolled patients in their study were clinically suspected urolithiasis and it would lead to a selection bias.

It has well known that CT examination has a high sensitivity and specificity for detecting fatty liver and renal stone disease [12,13]. In addition, CT examination also can quantify liver fat accumulation [8,15]. In our study, we reveal that the attenuation of liver parenchyma in patients with renal stone disease significantly lower than that in patients without renal stone disease ( $p < 0.05$ ). However, this disparity is too subtle to differentiate two groups

for clinical physicians in visual assessment. Furthermore, HU was no significant association with renal stone disease in multivariate analysis. Thus, we suggest that the severity of fatty liver has no association with renal stone disease.

The association between NAFLD and renal stone disease has received little attention. In the review of recent literature, oxidative and systemic metabolisms are compatible with stone formation [16]. The kidneys is an highly vulnerable organ damaged by reactive oxygen species, likely due to the abundance of long chain poly unsaturated fatty acids in the composition of renal lipids and systemic oxidative species can result in peroxidation of lipid that may have an effect in calcium oxalate stone formation [16]. Further data suggest that fatty liver may result in changes in urinary constituents, leading to an increased incidence of stone formation [17].

The strong point of our study is that we validated high relevance between fatty liver with renal stone disease on the basis of CT findings that have a higher sensitivity and specificity to detect fatty liver and renal stone disease than that of other imaging modality such as ultrasonography which can miss the renal stone disease in daily routine practice. Furthermore, it is noteworthy that the detection rate of renal stone disease more increased in patients with NAFLD (odds ratio: 5, 95% CI, 3–8.2) ( $p < 0.05$ ) than that of other study.

There were several limitations to our study. First, the possibility of selection bias should be considered because our results were based on a retrospective study design. However, we attempted to enroll all consecutive patients who met the inclusion criteria during the eligible period. Second, we did not performed interobserver and intraobserver reliability to evaluate NAFLD and renal stone disease.

In conclusion, the prevalence of renal stone disease in patients with NAFLD was significantly higher than that of patients without NAFLD and the presence of NAFLD may be considered to be an independent variable as a risk factor for renal stone disease.

#### Conflict of interests

Author declares that there are no conflict of interests.

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