Association of Non-Alcoholic Fatty Liver Disease with Renal Stone Disease detected on Computed Tomography

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) has been recognized as a liver manifestation of the metabolic syndrome. NAFLD is defined as the presence of at least 5% of the fat component in the liver without any other liver disease. 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. Recently, we noticed a concomitant diagnosis of both fatty liver and renal stones disease in same patient on the basis of computed 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.

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

Materials and Method: A total 250 patients who underwent abdomen-pelvis CT in 2016-17 were included in this study. All of the studies were performed on the same Dual Source CT. Fatty liver and nephrolithiasis were determined based on ultrasound and CT scan findings. 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.

Result: Among the 250 cases, there were 200 men (80%) and 50 women (20%).Association of fatty liver and stone was higher in men (28%) compare to female (12%).The association between NAFLD and nephrolithiasis was more prominent in cases less than 50 years of age than in those older than 50 years (p for interaction<0.001).

Conclusion: The present study indicates that the prevalence of Urolithiasis is significantly higher in the NAFLD than healthy subjects. This result suggests that NAFLD may be involved in the mechanism of onset of Urolithiasis.

Keywords: Renal Stone, Non Alcoholic Fatty Liver Disease, Urolithiasis, Computer Tomography, Concomitant Diagnosis, Association

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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 significant 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 epi-

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demiological 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 the 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 computed tomography (CT) finding in routine daily practice **(figure 2).** Literature reviews by using Pub med 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.

MATERIALS AND METHODS

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

From July 1, 2016 to July 31, 2017, a total of 250 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 radio opaque 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.

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 0.6 mm; rotation speed, 0.5 s; pitch, 0.8; reconstruction thickness, 3 or 5 mm; and no reconstruction interval.

Statistical analysis

To assess the association between fatty liver and renal stone dis-ease, 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.

RESULTS

Among the 250 cases, there were 200 men (80%) and 50 women (20%) as shown in **figure 1.** Out of 250 cases, only stones (renal, ureter, bladder) were found in 135 cases(54%), stone and NALFD in 100(40%), in 10 cases there was no stone and no fatty liver and in remaining 05 cases only fatty liver was found as shown in **table 1 & 2.**

The association between NAFLD and the nephrolithiasis was examined by sex. Out of 100 cases of NAFLD and stone, 70 were male and 30 were female. So association of fatty liver and stone was higher in men (28%) compare to female(12%). The association between

Table 1. Association between NAFLD and Nephrolithiasis

Total cases (n)	stones	stone + NAFLD	NAFLD	NIL
n = 250	135 (54%)	100 (40%)	05	10

Table 2. Showing sex and age distribution of NAFLD with stone cases

NAFLD+S	MEN	WOMEN	<50 years	> 50 years
100	70(28%)	30(12%)	65(26%)	35(14%)

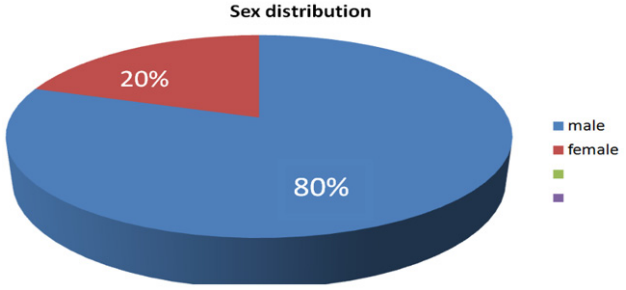

Figure 1. **Sex distribution of cases**

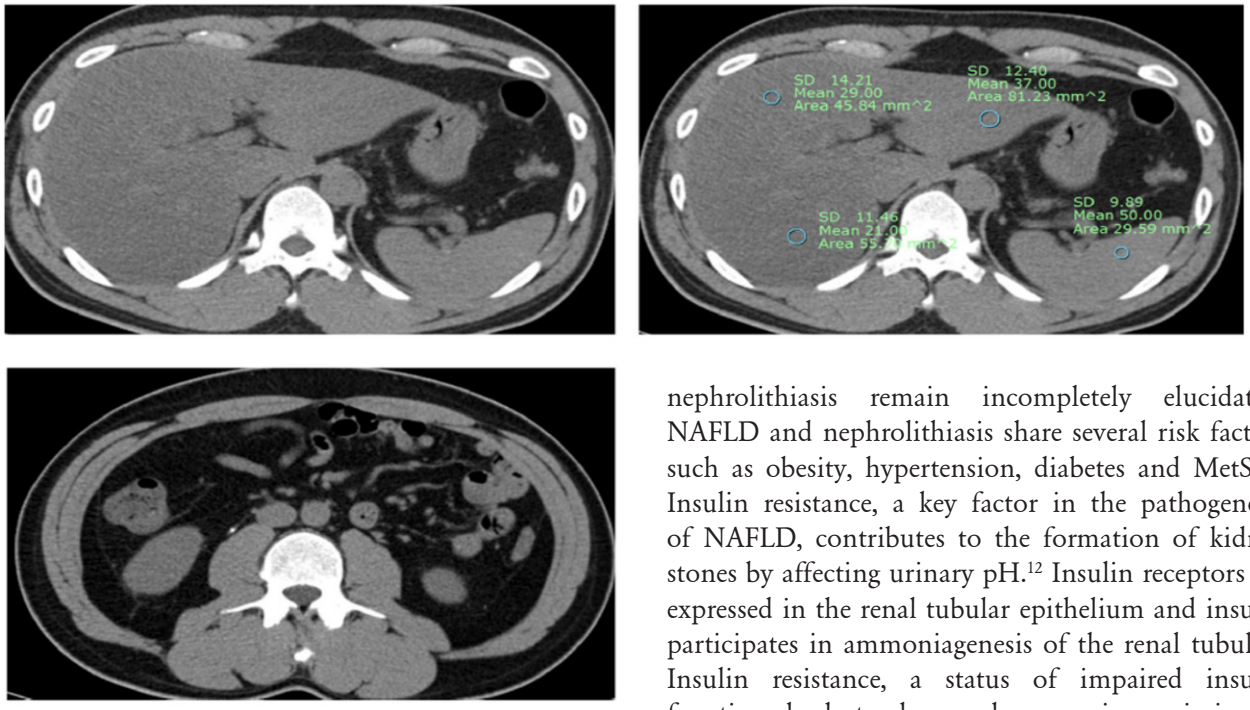

Figure 2. **Noncontrast scan images in a 55-year-old man show diffuse fatty liver and right ureter stone on noncontrast image. He visited our hospital with acute right flank pain, and his laboratory test revealed microscopic hematuria**

NAFLD and nephrolithiasis was more prominent in cases less than 50 years of age than in those older than 50 years (p for interaction<0.001). Out of 100 cases of NAFLD and stone, 65 cases were younger than 50 years and 35 above the 50 years.

DISCUSSION

In this study of young and middle-aged Indian adults, NAFLD was significantly associated with the development of nephrolithiasis in men(28%) compared to women (12%). For men, the modest association between NAFLD and incidence of nephrolithiasis persisted even after adjusting for possible confounders and metabolic factors, suggesting that NAFLD is an independent risk factor for nephrolithiasis in men. To the best of our knowledge, this is the first Indian cohort study to demonstrate that NAFLD is associated with an increased risk of nephrolithiasis.

A study at an Iranian medical center reported that patients with NAFLD showed a higher prevalence of nephrolithiasis.[11] However, this study used a cross-sectional design and did not adjust for possible confounders such comorbidities, lifestyle factors, and anthropometric measures, limiting the temporal and independent association between NAFLD and the development of nephrolithiasis.

The mechanisms whereby NAFLD contributed to nephrolithiasis remain incompletely elucidated. NAFLD and nephrolithiasis share several risk factors such as obesity, hypertension, diabetes and MetS.10 Insulin resistance, a key factor in the pathogenesis of NAFLD, contributes to the formation of kidney stones by affecting urinary pH.[12] Insulin receptors are expressed in the renal tubular epithelium and insulin participates in ammoniagenesis of the renal tubule.[13] Insulin resistance, a status of impaired insulin function, leads to decreased ammoniagenesis in the renal tubule,[13,14] resulting in acidic urine which may promote uric acid stones. In our study, the association between NAFLD and incident nephrolithiasis was evident even after adjustment for BMI, hypertension, diabetes, and HOMA-IR, and the association persisted among non-obese participants or among those with low hs CRP or with low HOMA-IR, suggesting that other mechanisms may influence the association between NAFLD and nephrolithiasis.

Kidney stone development can be attributed to reactive oxygen species (ROS) and inflammation.[15] Previous studies have suggested that stone formation can begin inside oxidatively damaged cells,[16] leading to cell death and the formation of membrane-bound vesicles which induce crystal nucleation.[17] ROS initiate a signaling pathway that produces macromolecules to activate or inhibit crystal nucleation, growth, and aggregation. Moreover, inflammatory markers and pro-inflammatory cytokines were found to be elevated in patients with nephrolithiasis.[10,18] In addition, lipotoxicity may contribute to renal cell damage, impaired renal cell function, and decreased ammoniagenesis.[19] Increased levels of pro-inflammatory molecules and lipotoxicity are also features of NAFLD.[20]

The association between NAFLD and nephrolithiasis was observed both in men and women but predominantly in men. These results are consistent with the previous study of Lonardo et al., which reported that risk factors for NAFLD vary according to sex.[14] The high prevalence of nephrolithiasis and NAFLD in men could partly explain this difference.[5,21] There may

also be other factors contributing to the occurrence of nephrolithiasis, such as estrogen status,[22] which could attenuate the influence of NAFLD on formation of renal stones. Estrogen may protect against kidney stone formation.[23] On the other hand, decreasing estrogen levels are associated with worsened metabolic status in postmenopausal women, leading to the formation of nephrolithiasis.[24] In addition, menopausal status can accelerate bone turnover, causing increased urine calcium excretion and decreased citrate excretion.[25] Due to the small number of postmenopausal women in our study, we were not able to perform stratified analysis by menopausal status. Further research is needed to examine the association between nephrolithiasis and NAFLD in women.

Additionally, the association between NAFLD and nephrolithiasis was more evident in the NAFLD group younger than 50 years of age. It is possible that the age-related increase in comorbidities may confound the association. Another possible explanation for the differences among the subgroups may by chance.

There are some limitations of this study. First, we did not adjust for diet, which is an important risk factor of nephrolithiasis. Second, clinical data related to symptoms of nephrolithiasis were not available. However, abdominal Ultrasound was performed routinely on all participants and nephrolithiasis was determined based on US findings. In this way we avoided recall bias and diagnosed asymptomatic nephrolithiasis. Third, information on the chemical composition of renal stones and specific renal stone type was not available for analysis. Fourth, we used US or non contrast ct scan for the diagnosis of fatty liver, while liver biopsy is regarded as the reference standard. A meta-analysis revealed that the overall sensitivity and specificity of US for the detection of moderate-to-severe fatty liver compared to histology was 84.8% and 93.6%, respectively. Although US assessment has an acceptable degree of diagnostic accuracy for steatosis, it cannot detect fatty infiltration below a threshold of 10%.[26] This type of error may result in underestimation of the true association between NAFLD and nephrolithiasis. Recently, semiquantitative US indices have been considered a reliable screening tool for metabolic derangements and might be helpful in understanding the pathogenesis of the NAFLD-nephrolithiasis association in future research, though these were not available in our study.[27] Further studies are needed using more sensitive and specific techniques to detect renal stones and NAFLD. Lastly, our study was conducted in small sample size in symptomatic young to middle-aged Indian adults. Thus, our findings may not be applicable when generalized to other populations.

In conclusion, in a cohort of Indian adults, NAFLD was associated with an increased risk for development of nephrolithiasis both in men and women but more predominantly in men. The association between NAFLD and nephrolithiasis was more prominent in cases less than 50 years of age than in those older than 50 years. This association persisted after controlling for possible confounders and other metabolic parameters, suggesting an independent role of NAFLD in the pathogenesis of nephrolithiasis.

END NOTE

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Conflict of Interest: None declared

Editor's Remarks: The authors have noticed a concomitant diagnosis of NAFLD and renal stones. The significance of this has been studied in a number of papers. This has not been studied in an Indian cohort. The results are interesting and should stimulate more studies. These studies will provide more validation in a wider perspective.

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