Original Article

Association between Non-alcoholic Fatty Liver Disease and Renal Stone Formation Based on Sex and Age

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ABSTRACT

Background:
Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome. According to previous studies, NAFLD can cause kidney dysfunction and the formation of urinary tract stones. In this study, the relationship between NAFLD and renal stone formation based on the sex and age of patients was investigated using non-contrast computed tomograms.

Material and Methods:
This study was performed in 2020 on 907 patients who were referred to Golestan Hospital and underwent computed tomography (CT) evaluation without contrast of the abdomen and pelvis. The statistical relationship between NAFLD and renal stone disease was assessed using the Chi-square test.

Results:
Participants in this study included 582 men (64.2%) and 325 women (35.8%). The frequency of NAFLD patients with renal stones was significantly higher than NAFLD patients without renal stones (82.1% vs 17.9%, $P<0.0001$). The frequency of renal stones in severe NAFLD was significantly higher than in patients with mild NAFLD (100% vs 78.8%; $P=0.008$). The risk of developing renal stones in patients with NAFLD disease increases with age compared with patients without NAFLD ($P<0.009$). Renal stones in patients with NAFLD were not affected by sex ($P=0.487$).

Conclusion:
These results show a significant association between NAFLD and renal stone formation in male and female populations. Also, this association is strengthened by the increase in the severity of NAFLD; therefore, NAFLD can be an independent risk factor for renal stone disease, and renal stone disease can be associated with metabolic syndrome or one of its components.

Keywords: Non-alcoholic fatty liver disease, renal stone disease, Non-contrast CT scan, metabolic syndrome

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome (1). When at least 5% of the liver tissue composition is fat without a history of alcohol consumption and any chronic liver disease, it is said that the patient has non-alcoholic fatty liver (2). According to the World Health Organization, the disease has affected more than 25% of the world's population (3). About 25% of people with NAFLD can develop non-alcoholic steatohepatitis (NASH), characterized by liver inflammation, and may progress to cirrhosis and hepatic failure (4). In most studies, the prevalence of NAFLD is highly correlated with the characteristics of metabolic syndrome and imposes high costs on healthcare organizations (5). Evidence suggests that NAFLD is associated with an increased risk of liver disease and can also act as a multisystem disease in some other organs, including the heart and urinary tract (6). Renal stone disease is caused by genetic and environmental factors of crystal deposition in the kidney and urinary tract (7). Recent studies show that renal stone disease is associated with obesity, diabetes, hypertension, and metabolic syndrome. These studies show that metabolic syndrome causes the formation of uric acid and calcium oxalate stones in the urinary tract by changing urine concentration (8). So, renal stone disease can be associated with metabolic syndrome or part of the metabolic syndrome (4). The exact mechanism has not yet been reported for the relationship between the two diseases. Due to the limited studies conducted to investigate the relationship between these two diseases, in this study, the relationship between NAFLD and renal stone disease based on the sex and age of patients was examined using non-contrast computed tomography (CT).

MATERIAL AND METHODS

This descriptive-analytical prospective study was performed on 907 patients referred to Golestan Hospital for non-contrast scanning in 2020. The following formula calculates the required sample size: $n=(z)^2\ p\ (1-p)\ /\ d^2$. The flowchart of the study is shown in Figure 1. This research was conducted after obtaining permission

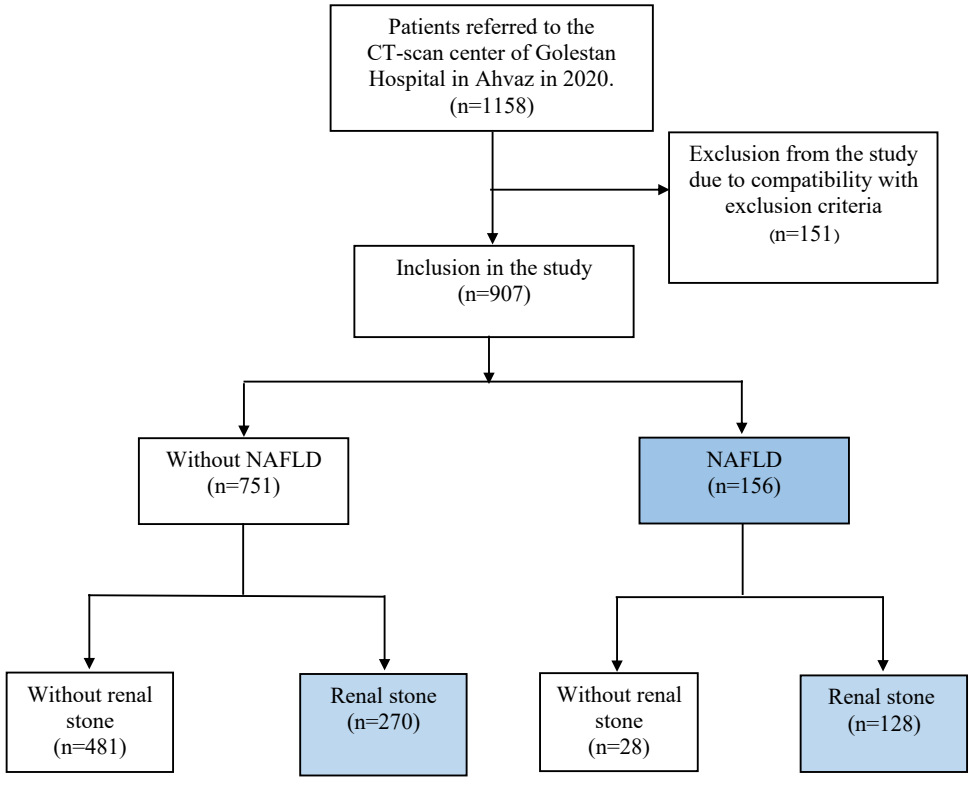

Figure 1. Flowchart of the study. Non-alcoholic fatty liver disease (NAFLD)

from the Research Council and approval of the Ethics Committee of Ahwaz University of Medical Sciences (code: IR.AJUMS.REC.1399.341). Informed and written consent was received from all patients before starting treatment. Inclusion criteria included: 1) NAFLD on a non-contrast CT scan, and 2) the presence of renal stones in the urinary tract, including kidneys, ureters, and bladder, in a non-contrast CT scan. Exclusion criteria include: 1) suboptimal quality of images due to beam hardening artifact, 2) other liver diseases including viral hepatitis, cirrhosis, hepatocellular carcinoma, and metastasis from primary cancer and splenectomy, 3) alcohol consumption (more than 30 g in men and 20 g in women daily), 4) continuous use of corticosteroids and 5) chemotherapy. Out of 907 patients, 156 had NAFLD based on diagnostic criteria in this study. Of the 156 patients with NAFLD, 128 had renal stones, and 28 had no renal stones.

CT scan method

Non-contrast abdominopelvic CT scan of patients was performed using a SIEMENS 64-slice CT scan machine made in Germany, model SOMATOM sensation. Patients were placed supine and scanned from 1 cm superior to the diaphragm to the lesser trochanters. Imaging data were obtained by LEONARDO software. the CT parameters were: tube voltage: 110 kvp, scan time: 7.9 sec, ref mAs: care dose 4D 150, rotation time: 0.5 sec, pitch: 0.8, collimation: 128×0.6 mm, slice thickness: 5 mm. A radiologist with 4 years of experience in non-contrast-enhanced abdominopelvic CT scan reports, who was blinded to patients' medical history, analyzed images to evaluate the presence of fatty liver or renal and urinary tract stones. To evaluate the presence of fatty liver, the radiologist measured the mean Hounsfield unit (HU) value of the liver parenchyma from three different parts: the right hepatic lobe and the left medial and lateral hepatic segments. If the average Hounsfield unit of the liver parenchyma in a non-contrast CT scan is at least 10 units less than the Hounsfield unit of splenic tissue, it indicates NAFLD (Figure 2). The severity of fatty liver disease was also determined. Non-alcoholic fatty liver was defined as lower liver parenchyma density than a port vein and inferior vena cava (IVC) in non-contrast CT scans. Hyperdense foci in the renal collecting system, ureter, and bladder indicated stones (Figure 3).

Statistical analysis

Inferential statistics were used to evaluate the study hypotheses, and the Chi-square test was used to evaluate the relationship between NAFLD and renal stones. The mean age was compared between the groups using an independent *t* test. The incidence of renal stones in patients with NAFLD and vice versa was evaluated by calculating the odds ratio and confidence interval (CI) of 95% and using logistic regression analysis. A P value less than 0.05 was considered a significant level. Statistical analysis of data was performed by SPSS software version 22.

RESULTS

In this study, based on inclusion criteria, 907 patients, including 582 men (64.2%) and 325 women (35.8%), participated with a mean age of 45.6±16.4 years (range of 15 to 89 years). The results related to the prevalence

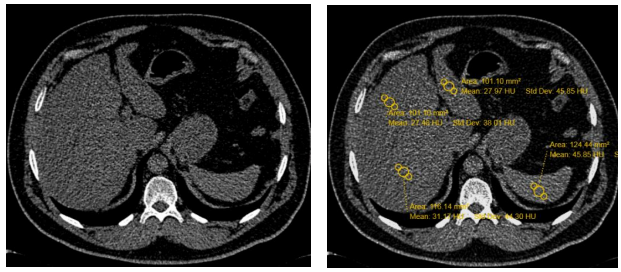

Figure 2. Non-contrast computed tomograms a 49-year-old man show fatty liver. The average HU of liver parenchyma is 28.87 HU, which is less more than 10 HU to spleen parenchyma HU

Figure 3. Non-contrast image of the same patient shows a stone at the left ureterovesical junction

of NAFLD and renal stones in the CT scan images of the study population are presented in Table 1. In this study, 156 patients (17.2%) had fatty liver, and 751 patients (82.8%) had no fatty liver. Also, 398 patients (43.9%) had renal stones. In 509 patients (56.1%), no renal stones were observed.

Association between NAFLD and renal stone disease and age

The frequency and percentage of patients with renal stones in people with NAFLD are shown in Table 2. The results showed that patients with renal stones had a higher percentage of NAFLD than those without renal stones (82.1% vs 36.0%; $P<0.0001$). As shown in the table, about 82.1% of patients with NAFLD had renal stones. On the other hand, the frequency of NAFLD patients with renal stones was equal to 128 (32.2%) cases ($P=0.0001$). These results show that the diagnosis of NAFLD using a non-contrast CT scan technique has a significant relationship with the risk of renal stone formation (OR: 8.14; 95% CI: 5.27–12.5)

(Table 2). This study shows that the prevalence of NAFLD and renal stones increase with age ($P=0.016$ and $P<0.0001$, respectively) (Table 2). Further analysis indicated that increasing age is associated with increased susceptibility to NAFLD patients for renal stone development ($P<0.009$).

Association between NAFLD and renal stone disease based on sex

The results related to the relationship between the prevalence of NAFLD and renal stones based on the sex of patients are reported in Table 3. The results show that in both men and women, the frequency of NAFLD in patients with renal stones is higher than in patients without renal stones ($P<0.0001$). In other words, renal stones in patients with NAFLD were not affected by sex ($P=0.487$).

Association between NAFLD and renal stone disease based on the severity of NAFLD

The results related to the relationship between renal stone disease and the severity of NAFLD disease are shown in Table 4. As can be seen, increasing the severity of the NAFLD increases the incidence of renal stones ($P=0.008$). The odd ratio of renal stone disease was reported at 0.81 (95% CI: 0.74-0.88) and 100 in patients with mild NAFLD and severe NAFLD, respectively.

DISCUSSION

The present study shows that NAFLD frequency is higher

Table 1. Absolute and relative frequencies of NAFLD cases and renal stone cases in a total of 907 (M=582 [64.2%], F=325 [35.8%]) using CT scan images

	Disease status	
Disease	**Positive**	**Negative**
NAFLD, n (%)	156 (17.2)	751 (82.8)
Renal stone, n (%)	398 (43.9)	509 (56.1)

Table 2. Association between NAFLD and renal stone diseases and age

	NAFLD (%)		*P* value	Renal Stone (%)		*P* value
Mean age±SD	Pos 48.6±15.8	Neg 45.0±17.1	0.016	Pos 50.3±16.9	Neg 41.9±15.9	<0.001
Renal Stone	128 (82.1) 270 6.0)	28 (17.9) 481 (64.0)	0.0001	-	-	-

Table 3. Association between NAFLD and Renal stone diseases based on the sex factor of patients

Sex	NAFLD	Renal stone (Pos) (%)	Renal stone (Neg) (%)	OR (95% CI)	*P* value
Male	NAFLD (+)	88 (81.5)	20 (18.5)	6.93 (4.12- 11.65)	<0.0001
	NAFLD (-)	184 (38.8)	290 (61.2)		
Female	NAFLD (+)	40 (83.3)	8 (16.7)	11.1 (4.98- 24.7)	<0.0001
	NAFLD (-)	86 (31.1)	191 (68.9)		

Table 4. Association between NAFLD and renal stone diseases based on the severity of NAFLD

NAFLD degree	Renal stone (Pos) (%)	Renal stone (Neg) (%)	Odd ratio (CI 95%)	*P* value
Mild	140 (78.8)	28 (21.2)	0.81 (0.74- 0.88)	0.008
Severe	24 (100)	0 (0)	100	

in patients with renal stones than in people without renal stones. Also, the diagnosis of NAFLD was significantly associated with an increased incidence of renal stones. The results also showed that the risk of renal stone disease in patients with NAFLD increases with age, possibly due to metabolic syndromes. Also, in both sexes, the risk of renal stones was higher in patients with NAFLD than in patients without NAFLD, but renal stones in patients with NAFLD were not affected by sex. The frequency of renal stones was higher in patients with more severe NAFLD. This association between NAFLD and renal stone disease has been reported in several studies in recent years (6,9) Consistent with the present study results, Chul and colleagues (2016), based on non-contrast CT scan images, showed the frequency of NAFLD in patients with renal stones was significantly higher than in patients without renal stones. Also, in that study, the diagnosis of NAFLD was associated with a higher risk of renal stone disease, and the incidence of renal stones was significantly higher in both men and women with NAFLD. These results are consistent with our study. However, in contrast to us, Chul and colleagues reported that the association of renal stones with NAFLD was not affected by the severity of fatty liver. The discrepancy between the results of studies requires further studies (10). Also, Einollahi and others (2013) reviewed 11,245 ultrasonographic reports. They reported that the incidence of renal stones in patients with NAFLD was significantly higher, and the diagnosis of NAFLD was associated with an increased risk of renal stone disease (6). Although the incidence of renal stones was higher in patients with non-alcoholic fatty liver than in patients without non-alcoholic fatty liver, this rate was lower than in the present study. Differences in the results observed in the present study compared with previous studies may be due to differences in the diagnostic performance of ultrasonography and CT. The sensitivity and specificity of routine CT in slice collimations less than 3 mm have been reported to be about 98% to 100% (11). The results of a meta-analysis study by Niemann and co-workers (2008) also reported 97% sensitivity in diagnosing renal stones by CT (12). Also, Ray and others (2010), in a prospective study using ultrasonography of the kidney after CT examination to diagnose renal stones, concluded that ultrasound accuracy was 65-77% (13). Therefore, it seems that ultrasonography leads to the diagnosis of fewer cases of renal stones. Also, in another similar result to our study, Paz and colleagues (2015) showed that the relationship between NAFLD and renal stone disease was statistically significant only in the male population and in people over 50 years. In contrast, no association was observed between young patients (under 50 years old) and the female population. The difference may be due to inclusion criteria. Also, all patients in that study were suspected of having renal stones, which could make a difference in the results (14). In another study by Zeina and others (2017), 508 patients with renal colic diagnosed by non-contrast CT scan showed a statistically significant association between nephrolithiasis and hepatosteatosis (15). Also, in a meta-analysis conducted by Qin and colleagues (2018), NAFLD was associated with an almost twice as high risk of developing renal stones compared with healthy individuals (16). In another study consistent with the present study, Arias and co-workers (2018), used CT images of 1010 patients and found that the frequency of diagnosis of NAFLD in patients with renal stones was significantly higher than in those without renal stones (17). Also, in contrast to the present study, Kaurav and others (2018) showed that the relationship between NAFLD and renal stones in men is significantly higher than in women, and also this relationship was observed in people aged under 50 years compared with patients over 50 years old (18). Results difference from the present study could be due to the small sample size in the study of Kaurav and others (2018) as well as differences in the characteristics of the study population. Reactive oxygen species (ROS) and oxidative stress play a major role in the pathogenesis

of NAFLD (19). Oxidative and systemic metabolites also have formed stones (20). It has also been reported that fatty acids can alter renal excretion, which is associated with the development of renal stones (21).

Overall, clinical and experimental data provide evidence for ROS production and oxidative stress in patients with NAFLD and renal stones, and oxidative stress may be jointly involved in the pathogenesis of both diseases (22,23). In addition, evidence suggests that renal stones are associated with a metabolic syndrome characterized by insulin resistance (24). Therefore, achieving the exact mechanism of this relationship requires more and more extensive research. Finally, it should be noted that the present study also faced some limitations, including failure to consider diet as an essential risk factor for renal stones. Data related to the chemical composition of renal stones and the type of renal stones were not examined. Therefore, with more studies, better results can be achieved.

CONCLUSION

The present study showed that the frequency of fatty liver in patients with kidney stones was higher than in those without kidney stones, and the frequency of kidney stones was higher in patients with NAFLD than those without fatty liver. Therefore, non-alcoholic fatty liver can be an independent risk factor for kidney stones. In addition to the significant relationship between fatty liver disease and kidney stones, it was observed that this relationship increases with the patient's age and the increasing severity of the NAFLD. Therefore, it is recommended that people with NAFLD, especially older people with severe disease, be carefully evaluated for kidney stones.

REFERENCES

1. Rinella ME. Nonalcoholic fatty liver disease a systematic review. JAMA; 2015;313: 2263–73.
2. Mahady SE, Adams LA. Burden of non-alcoholic fatty liver disease in Australia. J Gastroenterol Hepatol. 2018;33:1–11.
3. Hamaguchi M, Takeda N, Kojima T, Ohbora A, Kato T, Sarui H, et al. Identification of individuals with non-alcoholic fatty liver disease by the diagnostic criteria for the metabolic syndrome. World J Gastroenterol. 2012;18(13):1508-16.
4. Huang T, Behary J, Zekry A. Non-alcoholic fatty liver disease: a review of epidemiology, risk factors, diagnosis and management. Intern Med J. 2020;50(9):1038–47.
5. Mahady SE, Adams LA. Burden of non-alcoholic fatty liver disease in Australia. J Gastroenterol Hepatol. 2018;33:1–11.
6. M Younossi Z , Otgonsuren M , Henry L , Venkatesan C , Mishra A , Erario M, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009 . Hepatology. 2015;62(6):1723-30.
7. Targher G, Chonchol M, Pichiri I, Zoppini G. Risk of cardiovascular disease and chronic kidney disease in diabetic patients with non-alcoholic fatty liver disease: Just a coincidence? J Endocrinol Invest. 2011;34(7):544-51.
8. Wang K, Ge J, Han W, Wang D, Zhao Y, Shen Y, et al. Risk factors for kidney stone disease recurrence: a comprehensive meta-analysis. BMC Urol. 2022;22(1):1–13.
9. Chang Y, Ryu S, Sung E, Woo HY, Oh E, Cha K, et al. Nonalcoholic fatty liver disease predicts chronic kidney disease in nonhypertensive and nondiabetic Korean men. Metabolism. 2008;57(4):569–76.
10. Nam IC. Association of non-alcoholic fatty liver disease with renal stone disease detected on computed tomography. Eur J Radiol Open. 2016;3:195–9.
11. Heidenreich A, Desgrandschamps F, Terrier F. Modern Approach of Diagnosis and Management of Acute Flank Pain: Review of All Imaging Modalities. Eur Urol. 2002;41(4):351–62.
12. Niemann T, Kollmann T, Bongartz G. Diagnostic Performance of Low-Dose CT for the Detection of Urolithiasis: A Meta-Analysis. 2012;191(2):396–401.
13. Ray AA, Ghiculete D, Pace KT, Honey RJDA. Limitations to Ultrasound in the Detection and Measurement of Urinary Tract Calculi. Urology. 2010 ;76(2):295–300.
14. Paz D GL. Association of renal stone (urolithiasis) with nonalcoholic fatty liver (NAFL). ECR 2015. Poster Number:C-2056.
15. Zeina AR, Goldenberg L, Nachtigal A, Hasadia R, Saliba W. Association between nephrolithiasis and fatty liver detected on non-enhanced CT for clinically suspected renal colic. Clin Imaging. 2017 May 1;43:148–52.
16. Qin S, Wang S, Wang X, Wang J. Non-alcoholic fatty liver disease and the risk of urolithiasis: A systematic review and meta-analysis. Medicine. 2018;97(35):e12092.
17. ARIAS C LF. Renal lithiasis and Fatty Liver Disease, is there any relationship? ECR 2018. Poster Number:C-3221.
18. Kaurav Rustam Singh VS. Association of Non-Alcoholic Fatty Liver Disease with Renal Stone Disease detected on Computed Tomography | Kerala Medical Journal. Kerala Medical Journal. 2018;11(1):18–22.
19. Musso G AR. Antioxidant Therapy and Drugs Interfering with Lipid Metabolism: Could They Be Effective in NAFLD Patients? Ingenta Connect. Curr Pharm Des. 2013;19(29):5297–313.
20. Schwille P, Schmiedl A, Wipplinger J. Idiopathic

Recurrent Calcium Urolithiasis (IRCU): variation of fasting urinary protein is a window to pathophysiology or simple consequence of renal stones in situ? A tripartite study in male patients providing insight into oxidative metabolism as possible driving force towards alteration of urine composition, calcium salt crystallization and stone formation. Eur J Med Res. 2009;14(9):378–92.
21. Baggio B, Budakovic A, Priante G, Gambaro G, Manzato E, Khan S. Dietary fatty acid supplementation modulates the urinary excretion of calcium and oxalate in the rat. Insight into calcium lithogenesis. Nephron. 2002;91(3):486–91.
22. Sumida Y, Niki E, Naito Y, Yoshikawa T. Involvement of free radicals and oxidative stress in NAFLD/NASH. Free Radic Res . 2013;47(11):869-80.
23. Khan SR. Reactive Oxygen Species as the Molecular Modulators of Calcium Oxalate Kidney Stone Formation: Evidence from Clinical and Experimental Investigations. J Urol. 2013;189(3):803–11.
24. Domingos F, Serra A. Metabolic syndrome: A multifaceted risk factor for kidney stones. Scand J Urol. 2014;48(5):414-9.