Original Article

Association between non-alcoholic fatty liver disease and urolithiasis: a cross-sectional study

Asociación entre la enfermedad del hígado graso no alcohólico y la urolitiasis: un estudio transversal

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Abstract

Background: urolithiasis, the formation of kidney stones, is associated with chronic conditions such as metabolic syndrome, which increases the risk of uric acid and calcium oxalate stones. Based on CT scan findings, this study aims to investigate the association between non-alcoholic fatty liver disease (NAFLD) and urolithiasis.

Method: over two years, a cross-sectional comparative study was conducted at Razi Hospital in Birjand, Iran. Participants were patients aged 16 to 80 presenting with renal colic who underwent non-contrast abdominopelvic CT scans. Exclusion criteria included other liver diseases, excessive alcohol consumption, and a history of splenectomy. Data were collected using a structured checklist and analyzed for the presence of fatty liver and kidney stones.

Results: the study included 911 participants, with a mean age of 47.88 years (SD = 16.48). Among the participants, 80 had fatty liver disease, and 50 of these had kidney stones. In contrast, of the 831 participants without fatty liver, 356 had kidney stones. The association between fatty liver and kidney stones was significant ($p < 0.001$). Gender-stratified analysis showed that males with fatty liver had a higher incidence of kidney stones compared to females ($p < 0.001$ for males, $p = 0.631$ for females).

Conclusion: the study confirms a significant association between NAFLD and urolithiasis, particularly in males. The findings suggest that screening for kidney stones in patients with fatty liver disease might be beneficial. Addressing underlying metabolic disorders could help mitigate the risk of developing both conditions.

Keywords:
Non-Alcoholic Fatty Liver Disease, Urolithiasis, Kidney Stones, Metabolic Syndrome, Insulin Resistance, CT Scan

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Resumen

Antecedentes: la urolitiasis, la formación de cálculos renales, se asocia con enfermedades crónicas como el síndrome metabólico, que aumenta el riesgo de cálculos de ácido úrico y oxalato de calcio. Con base en los hallazgos de la tomografía computarizada (TC), este estudio busca investigar la asociación entre la enfermedad del hígado graso no alcohólico (EHGNA) y la urolitiasis.

Método: se realizó un estudio comparativo transversal durante dos años en el Hospital Razi de Birjand, Irán. Los participantes fueron pacientes de 16 a 80 años con cólico renal, sometidos a tomografías computarizadas abdominopélvicas sin contraste. Los criterios de exclusión incluyeron otras enfermedades hepáticas, consumo excesivo de alcohol y antecedentes de esplenectomía. Los datos se recopilaron mediante una lista de verificación estructurada y se analizaron para detectar la presencia de hígado graso y cálculos renales.

Resultados: el estudio incluyó a 911 participantes, con una edad media de 47,88 años (DE = 16,48). De ellos, 80 presentaban enfermedad del hígado graso y 50 cálculos renales. En contraste, de los 831 participantes sin hígado graso, 356 presentaban cálculos renales. La asociación entre hígado graso y cálculos renales fue significativa ($p < 0,001$). El análisis estratificado por género mostró que los hombres con hígado graso presentaron una mayor incidencia de cálculos renales en comparación con las mujeres ($p < 0,001$ para hombres, $p = 0,631$ para mujeres).

Conclusión: el estudio confirma una asociación significativa entre la EHGNA y la urolitiasis, especialmente en hombres. Los hallazgos sugieren que la detección de cálculos renales en pacientes con enfermedad del hígado graso podría ser beneficiosa. Abordar los trastornos metabólicos subyacentes podría ayudar a mitigar el riesgo de desarrollar ambas afecciones.

Palabras clave: Enfermedad del hígado graso no alcohólico, Urolitiasis, Cálculos renales, Síndrome metabólico, Resistencia a la insulina, Tomografía computarizada

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of at least 5 % triglycerides in hepatocytes, making it the most prevalent liver disease globally. Distinct from alcoholic fatty liver disease (AFLD), NAFLD encompasses a spectrum of conditions ranging from simple hepatic steatosis to more severe forms that are risk factors for fibrosis, cirrhosis, and hepatocellular carcinoma. NAFLD is strongly linked to obesity, insulin resistance, metabolic syndrome, chronic kidney disease, and cardiovascular diseases.[1]

The gold standard for diagnosing NAFLD is liver biopsy, which classifies the disease into mild (triglyceride level 5-33 %), moderate (triglyceride level 34-66 %), and severe (triglyceride level >66 %). However, due to the invasive nature and potential complications of liver biopsies, non-invasive methods like ultrasound are often employed. Additionally, CT scans showing decreased liver parenchymal density in fatty liver patients are also effective for diagnosing NAFLD. Non-contrast CT scans can identify fatty liver using indices such as liver-spleen density differences.[2,3]

Urolithiasis, a common renal disease, involves the deposition of crystals in the renal medulla and collecting ducts.[4] The formation of kidney stones is influenced by both intrinsic and extrinsic factors and is associated with chronic conditions such as chronic kidney disease, diabetes, hypertension, and metabolic syndrome.[5–8] Metabolic syndrome, in particular, induces changes in urine composition that increase the risk of uric acid and calcium oxalate stones.[9]

Cross-sectional studies indicate a significantly higher prevalence of urolithiasis in patients with NAFLD, though the mechanisms linking the two are not fully understood. Potential factors include hepatic steatosis, insulin resistance, and oxidative stress.[10]

Recent studies have shown that NAFLD is significantly associated with an increased risk of urolithiasis. A meta-analysis of observational studies found that patients with NAFLD had a 1.73-fold increased risk of developing urolithiasis compared to those without NAFLD(10).10 The exact mechanisms linking NAFLD to urolithiasis remain unclear, but several potential pathways have been proposed. These include the role of reactive oxygen species (ROS) production and oxidative stress, which can promote the formation of kidney stones by altering urinary constituents and reducing antioxidant capacity.[11]

Furthermore, metabolic syndrome, closely associated with NAFLD, contributes to an increased risk of uric acid and calcium oxalate stone formation. Insulin resistance, a key feature of metabolic syndrome, interferes with renal acid excretion and purine metabolism, leading to unduly acidic urine pH and reduced urinary ammonium excretion.[12] This metabolic disturbance may create a favorable environment for kidney stone formation in patients with NAFLD. Therefore, careful monitoring and management of urolithiasis in patients with NAFLD are recommended to mitigate the risk of kidney stone development and associated complications.[9,13]

While several prior studies, including the study by Qin *et al.* (2018),[14] have identified a statistical association between NAFLD and urolithiasis, many of these rely on pooled analyses with heterogeneous definitions and diagnostic modalities. Our study adds value by employing a uniform diagnostic modality (non-contrast CT scans) for both NAFLD and kidney stones in a large Middle Eastern cohort, which remains underrepresented in the literature. Moreover, we provide a gender-stratified analysis and adjust for confounders through multivariate regression, offering clearer clinical insight into the nature of this association in a real-world population.

This study aims to investigate the association between non-alcoholic fatty liver disease (FLD) and urolithiasis based on CT scan findings, seeking to elucidate the potential clinical implications of this relationship

Method

Study Design

This study employed a cross-sectional comparative analysis to investigate the prevalence of kidney stones among patients with FLD. The study was conducted over two years at the hospital, with a sample size selected using a consensus method.

Participants

The study included patients aged 16 to 80 who presented with renal colic and underwent non-contrast abdominopelvic CT scans. Key exclusion criteria were established to minimize confounding factors, excluding individuals with other liver diseases (e.g., viral hepatitis, cirrhosis, hepatocellular carcinoma, liver metastases), excessive alcohol consumption, or a history of splenectomy.

Data Collection

Upon arrival at the emergency department, patients were evaluated by an emergency medicine specialist. Those requiring further investigation for renal colic were referred to the radiology department for non-contrast CT scans of the abdomen and pelvis. Outpatient clinic patients meeting the study criteria were similarly referred for CT scans.

A radiology resident explained the study procedures and objectives to each participant, obtained written informed consent, and collected data using a structured checklist. This checklist captured demographic details (age and gender) and documented the presence of both fatty liver and kidney stones.

CT imaging was performed with a 16-slice CT scanner using the following parameters: tube voltage of 130 kVp, rotation speed of 1 second, pitch of 1.3, and a reconstruction thickness of 5 mm. The scan range extended from the lower lungs to the pubic symphysis.

A radiology resident, blinded to the clinical data, reviewed the CT images to record the presence of fatty liver and kidney stones on the study checklist.

Statistical Analysis

Data were analyzed using SPSS version 26. Descriptive statistics (mean, SD, frequency, percentage) were used to summarize participant characteristics. Chi-square tests assessed the association between fatty liver and kidney stones overall and by gender. Binary logistic regression was performed to evaluate the relationship between fatty liver disease and the presence of kidney stones, adjusting for potential confounders. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in strict accordance with the STROBE guidelines for cross-sectional studies. Participants provided informed consent after receiving detailed explanations of the study procedures. Patient confidentiality was rigorously maintained, and all data were anonymized before analysis. The study was approved by the Ethics Committee of Birjand University of Medical Sciences (IR.BUMS.REC.1401.112). All participants provided written informed consent. Data were anonymized and securely stored.

Results

A total of 911 participants were included in the study to examine the prevalence of kidney stones among individuals with fatty liver disease. The participants ranged in age from 16 to 80 years, with a mean age of 47.88 years (SD = 16.48) and a median age of 47 years. Among the total sample, 831 individuals did not have fatty liver, while 80 were diagnosed with the condition. Of those without fatty liver, 475 did not have kidney stones, and 356 did. Among participants with fatty liver, 30 did not have kidney stones and 50 did (Table 1).

Table 1. Crosstabulation of fatty liver and kidney stones

Fatty Liver	Kidney Stones: No	Kidney Stones: Yes	Total	Chi-Square
No	475	356	831	$P < 0.001$
Yes	30	50	80	
Total	505	406	911	

In the subgroup of 405 female participants, 373 did not have fatty liver, and 32 had fatty liver. Among those without fatty liver, 260 did not have kidney stones, and 113 did. Of the 32 females with fatty liver, 21 did not have kidney stones and 11 did (Table 2). Among the 506 male participants, 458 were without fatty liver, and 48 were diagnosed with fatty liver. Of the males without fatty liver, 215 did not have kidney stones, and 243 did. Among males with fatty liver, nine did not have kidney stones, whereas 39 had kidney stones (Table 3).

Table 2. Crosstabulation of fatty liver and kidney stones in female participants

Fatty Liver	Kidney Stones: No	Kidney Stones: Yes	Total	Chi-Square
No	260	113	373	$P = 0.631$
Yes	21	11	32	
Total	281	124	405	

Table 3. Crosstabulation of fatty liver and kidney stones in male participants

Fatty Liver	Kidney Stones: No	Kidney Stones: Yes	Total	Chi-Square
No	215	243	458	$P < 0.001$
Yes	9	39	48	
Total	24	282	506	

To account for potential confounding factors, a multivariate logistic regression analysis was conducted. The dependent variable was the presence of kidney stones (yes/no), and the independent variables included NAFLD status, age, and gender.

The analysis indicated that having NAFLD was significantly associated with higher odds of having kidney stones (AOR = 2.56, 95 % CI: 1.63–4.03, $p < 0.001$), after adjusting for age and gender. Male gender and older age were also independently associated with increased risk (Table 4).

Table 4. Logistic regression predicting kidney stone presence

Variable	β (SE)	AOR (95 % CI)	p-value
NAFLD (Yes vs No)	0.94 (0.23)	2.56 (1.63–4.03)	<0.001
Male (vs Female)	0.68 (0.18)	1.98 (1.40–2.79)	<0.001
Age (per year)	0.015 (0.006)	1.02 (1.00–1.03)	0.011

Discussion

The results of this study reveal a significant association between FLD and the prevalence of kidney stones, underscoring a potential clinical linkage between these two conditions. Among the 911 participants, individuals with FLD exhibited a notably higher prevalence of kidney stones compared to those without FLD. These findings align with previous research by Nam et al. and Einollahi et al., both of which reported an increased risk of renal stone formation in individuals with NAFLD. Specifically, Nam et al. identified a higher frequency of kidney stones in patients with NAFLD diagnosed via computed tomography, while Einollahi et al. reported that the prevalence of urolithiasis was 17 % in those with NAFLD, compared to only 8 % among individuals with healthy livers.(9,15)

Further supporting these findings, Kaurav and Vasudevan observed a significant association between NAFLD and nephrolithiasis in a cohort study, indicating that the prevalence of urolithiasis is higher in patients with NAFLD compared to those without.(16) Another study by Umbro et al. confirmed the association, noting that NAFLD patients showed a higher incidence of chronic kidney disease (CKD), which often involves stone formation.(17)

Our gender-stratified analysis showed that male patients with fatty liver had a higher incidence of kidney stones compared to females. This finding is corroborated by the study by Chang *et al.* (2008), which found a stronger association between NAFLD and CKD in males than females. Similarly, our data indicated that 81.3 % of males with fatty liver had kidney stones compared to 34.4 % of females with fatty liver. This gender disparity highlights a potential difference in the pathophysiology of these conditions between men and women.(18) This could be due to differences in metabolic profiles and hormone levels between genders, which influence the pathophysiology of both NAFLD and nephrolithiasis.(19)

To ensure that the observed association between NAFLD and urolithiasis was not confounded by demographic factors, we performed a multivariate logistic regression analysis adjusting for age and gender. The results demonstrated that NAFLD independently predicted a significantly higher risk of kidney stones, with an adjusted odds ratio (AOR) of 2.56. This means that patients with NAFLD were more than twice as likely to develop kidney stones compared to those without NAFLD, even after controlling for age and gender.

Furthermore, male gender was associated with nearly double the odds of kidney stone formation compared to females, which supports our gender-stratified findings. Increasing age was also a modest but significant predictor.

These findings strengthen the argument for a potential biological link between NAFLD and urolithiasis beyond demographic correlates. It suggests that the co-occurrence of these conditions may be driven by shared metabolic and inflammatory pathways, such as insulin resistance and oxidative stress, rather than merely coincidental demographic overlap.

Several biological mechanisms could explain the observed association between FLD and kidney stones. Metabolic syndrome, which includes conditions such as obesity, hypertension, and insulin resistance, is a common link between NAFLD and renal stone disease. Insulin resistance can lead to hyperinsulinemia, promoting renal calcium reabsorption and reducing urinary citrate excretion, thereby increasing the risk of kidney stone formation. Additionally, oxidative stress and lipid peroxidation, prevalent in NAFLD, can lead to changes in urinary composition, promoting stone formation.(20) This is supported by the findings of Wilechansky et al. and Musso et al., who described the role of metabolic and inflammatory factors in linking NAFLD with kidney disease.(21,22)

Clinical Implications

The findings of this study have significant clinical implications. Given the high prevalence of both FLD and kidney stones, healthcare providers should consider the potential co-existence of these conditions in patients. Screening for kidney stones in patients diagnosed with FLD might be warranted to ensure early detection and management. Furthermore, addressing underlying metabolic disorders through lifestyle interventions and medical management could help mitigate the risk of developing these conditions. Studies indicate that managing factors such as obesity, diabetes, and hypertension could reduce the prevalence and impact of both FLD and kidney stones.(23–25)

Contradictory Evidence

The findings of our study are consistent with the results of Qin *et al.* (2018),(14) who reported a pooled odds ratio of 1.73 in favor of a significant association between NAFLD and kidney stones. However, unlike most studies included in that meta-analysis, which varied in diagnostic criteria and population characteristics, our study used CT scan-based diagnosis, ensuring greater diagnostic accuracy and consistency. Additionally, by focusing on a Middle Eastern population, we contribute region-specific evidence that has been underreported in existing literature. The gender-stratified analysis and incorporation of logistic regression modeling to control for age and sex further enhance the clinical interpretability of our findings and provide additional nuance not extensively explored in Qin's meta-analysis.

Despite the strong association observed in our study, it is important to consider contradictory evidence from recent research. A two-sample Mendelian randomization analysis conducted by researchers excluded a causal relationship between non-alcoholic fatty liver disease and kidney stones, suggesting that the observed association might be due to confounding factors rather than a direct causal link. [26] This analysis highlights the complexity of the relationship between NAFLD and kidney stones and underscores the need for further research to elucidate the underlying mechanisms and potential confounders. Understanding these nuances is crucial for developing targeted prevention and treatment strategies for patients affected by both conditions.

Limitations and Future Research

This study has several limitations that must be considered when interpreting the results. The study was conducted at a single hospital, which may limit the generalizability of the findings to other populations and settings. Second, there are other confounding factors that were not included in the checklist that can affect the final results; the use of multivariate tests to measure the effects of other confounding factors seems the path for future research. Additionally, future research should aim to elucidate the biological pathways linking NAFLD and kidney stones and explore potential therapeutic targets. Longitudinal studies are needed to determine the causal relationship between these conditions and assess the long-term impact of interventions aimed at reducing fatty liver and kidney stone risk. Also, body mass index (BMI) and other metabolic indices were not recorded, which may confound the observed association.

Conclusion

The results of this study are consistent with findings from other similar studies conducted in different parts of the world, indicating a potential association between NAFLD and urolithiasis. A similar pathophysiological pathway and the role of reactive oxygen species and oxidative stress may be the potential cause of this association. Considering the increasing prevalence of NAFLD, non-alcoholic fatty liver disease, and other metabolic syndrome-related diseases can impose significant healthcare and treatment costs on the healthcare system. This underscores the need for greater attention to planning for healthier lifestyles, especially among high-risk populations**.**

Conflict of interest

There is no conflict of interest-

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