Relationship Between Urolithiasis and Fatty Liver Disease: Findings in Computed Tomography

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ABSTRACT

There are no studies that allow a joint diagnostic or therapeutic intervention for the treatment of fatty liver and urolithiasis, perhaps because it is not known if there is an association between these 2 diseases. We aimed to identify a relationship between renal lithiasis and fatty liver disease by examining for common factors that could be used to reduce their incidence and complications. Our study supports the association of fatty liver and urolithiasis. Given the increase in frequency of these 2 diseases, we believe there is a common pathway within the malabsorptive and metabolic syndromes, thus leading for a new field of research to find a mechanism that allows timely interventions.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a given term to define a spectrum of liver entities ranging from simple steatosis to non-alcoholic steatohepatitis, with the eventual development of non-cholestatic nonalcoholic cirrhosis and the risk of hepatocellular carcinoma (1). According to the variability of the different types of population studies carried out (2), NAFLD affects a range from 1% to 51% of the population. Moreover, nephrolithiasis is considered a problem with a significant economic and health burden. Its prevalence has increased in recent years, in parallel to the increase in the prevalence of metabolic syndrome. Recent evidence has suggested a close link between NAFLD and the increased risk of urolithiasis; however, the biological mechanism remains unclear (3, 4). Among the risk factors associated with NAFLD, the most important is the syndrome of insulin resistance and the metabolic syndrome. Diabetes mellitus and dyslipidemias are considered primary causes (5, 6, 7). Liver biopsy is the gold standard for the diagnosis of NAFLD, but this test is an invasive procedure and not free of complications. Computed tomography (CT) is a noninvasive method with rapid acquisition of images that allows quantitative evaluation of the diagnosis of NAFLD; therefore, it is useful in clinical practice and offers monitoring and follow-up of patients (8, 9). To the best of our knowledge, there are no studies on joint diagnostic or therapeutic intervention for the treatment of fatty liver and urolithiasis, perhaps because it is not known if there is an association between these two diseases. The purpose of this study was to identify the relationship between renal lithiasis and fatty liver disease by examining for common factors that could be used to reduce their incidence and complications.

METHODS

A prevalence study was carried out by evaluating abdominal tomography studies performed in a population consisting of individuals of age >18 years; these images were assessed at the radiology and diagnostic images department of the Carlos Ardila Lülle Clinic (Santander, Colombia) during a 12-month period. A sample of 1010 abdominal CTs (performed using Aquilion 64 multislice helical acquisition system, Toshiba Medical Systems) was obtained after verification of the following exclusion criteria: pregnant women, chronic renal failure, renal or urinary tract malformations, hepatosplenomegaly, splenectomy, focal liver disease , a history of liver/kidney transplant, dialytic therapy, and a study to rule out a neoplasia or in treatment for neoplasia.

The CTs were performed using protocols detailed in the following sections.

Protocol for Non-Contrast Urinary Tract Computed Tomography

Non-contrast Tomography with 5 mm cuts is taken from the lower edge of the diaphragmatic dome to the pelvic floor, with distended bladder. Multiplanar coronal and sagittal reconstructions are made with 3 mm cuts.

Protocol for Computed Tomography of the Abdomen

The protocol for CT of abdomen included the following steps:

- Tomography with and without intravenous contrast with 5-mm cuts from the lung base to the pelvic floor.
- Data were obtained using noncontrast CT examinations. Demographic information of age and gender was collected. Additional or incidental findings such as diverticular disease in the colon, cholelithiasis, or atherosclerosis of the abdominal aorta were also recorded.
- Liver density was determined using a circular region of interest (ROI) parameter of 1 cm in diameter in the right lobe, making an isolated measurement of each segment and after that an average of the value obtained in each hepatic segment was done for a final single value.
- Spleen density was obtained by computing and averaging 3 measurements using a 1-cm-diameter circular ROI at the upper, middle, and lower segments.
- The diagnosis of fatty liver was made by using quantitative techniques, obtaining the difference of liver–spleen densities. If the result is <5 UH, fatty liver is absent. Results between 5 UH and −10 UH are classified as mild-to-moderate steatosis and results lower than −10 UH are considered moderate-to-severe steatosis.

Urolithiasis was classified as macrolithiasis and microlithiasis having as a discriminatory value stones less than 2 mm in greatest diameter. Its location in the urinary system from the renal calyces, the ureteral segments and the bladder was also described. To determine the density of the renal stones, a circular ROI was used that would occupy the largest diameter of the stone surface, and the values were averaged once 3 measurements were obtained. In a window for bone, the intrinsic characteristics of the calculation are described taking into account its homogeneity or heterogeneity. The size of the stone was determined based on 3 dimensions and the volume of these measurements.

Statistical Analysis

For the analysis, the information was entered into a database, typed in duplicate, and validated with the STATA 10 statistical package. An exploratory descriptive analysis of the imaging findings was conducted through measures of central tendency and dispersion for the quantitative variables and through proportions with 95% CIs for qualitative variables. A bivariate analysis was performed, calculating relative prevalence, then a multivariate analysis was performed using a regression method to adjust their combined effects, and finally the adjusted relative prevalence of each detected attitude was calculated. The input and output of variables in the regression method were performed based on the criteria established by Sander Greenland (23).

RESULTS

We analyzed 1010 CT scans of 510 women and 500 men who met the inclusion criteria, out of an overall of 4938 CT scans performed by the radiology department during a 12-month period. Fatty liver disease was found in 458 scans, representing 45.3% of the cases, and urolithiasis was observed in 676 images, corresponding to 66.9% of the cases (Figure 1). The coexistence of both findings is more frequent in men, while in the isolated form,
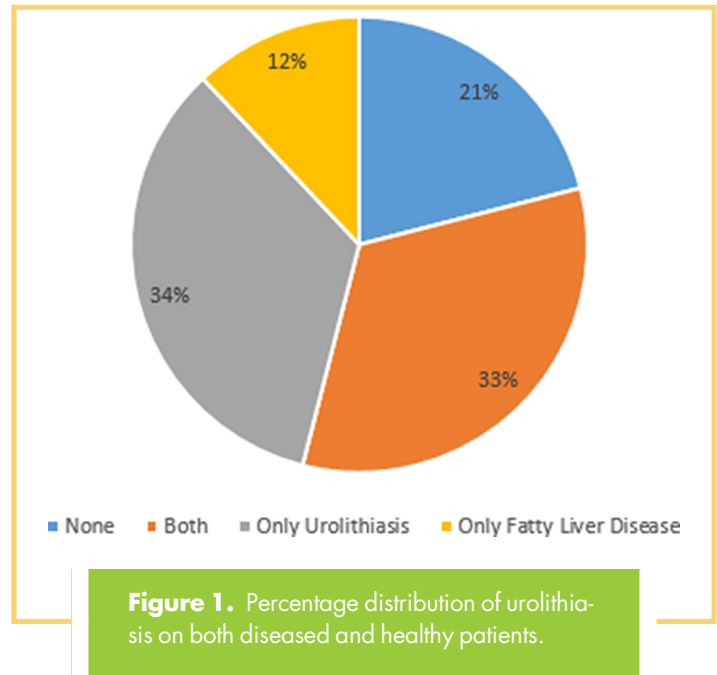
Figure 1. Percentage distribution of urolithiasis on both diseased and healthy patients.

it predominates in women. The percentage of CT without urolithiasis and without Fatty liver Disease was 27% in women and 14% in men.

We found that 337 patients, corresponding to 33% of the cases, presented simultaneously urolithiasis and hepatic steatosis. Half of the patients with urolithiasis also presented hepatic steatosis and approximately two-thirds of the patients without urolithiasis had a nonsteatotic liver, with a PR of 1.37, $P < .0001$, and when adjusted for age and gender, the PR is 1.29, $P < .002$−a statistically significant finding (Table 1).

We classified the severity of steatosis in ranges of absence of steatosis, mild/moderate, and moderate/severe, according to the difference in the hepato/splenic densities. We found a progressive simultaneous increase in the percentage of urolithiasis, with 61.4% for healthy patients and 71% for those with steatosis in the mild-to-moderate range and 75.7% for patients classified as having severe steatosis (Table 2).

The density of the kidney stones was divided into higher or lower than 500 UH, to differentiate these by their composition given that those <500 UH contain primarily uric acid. The density of the stone is not associated with hepatic steatosis (PR = 0.88; 95%CI (0.75–1.01) $P = .12$). The intrinsic homogeneity and heterogeneity characteristics of the calculation related to hepatic steatosis had an associated PR of 0.85, 95%CI (0.71–1.02), $P = .068$.

DISCUSSION

The association of urolithiasis and hepatic steatosis has been poorly studied. In our study, we found this association in 33% of the total number of patients, a result similar to the result of the study of Einollahi B et al. (10) (with a prevalence of 30%), conducted on 11 245 patients in whom ultrasonography was used to determine the presence of hepatic steatosis and urolithiasis. It is interesting to mention that if we evaluate only patients with

Table 1. Association between Fatty Liver and Urolithiasis

	Fatty Liver Disease	Healthy Liver	
Urolithiasis	337 (49.8%)	339 (50.2%)	676 (100%)
Without Urolithiasis	121 (36.2%)	213 (63.8%)	334 (100%)
Overall	458 (45.4%)	552 (54.6%)	1010 (100%)

PR crude = 1.37 (95%CI, 1.17 a 1.62; $P < .001$), PR adjusted* = 1.29 (95%CI, 1.1 a 1.53; $P = .002$) (*By gender and age).
Abbreviation: PR, prevalence ratio.

hepatic steatosis, the frequency of urolithiasis is seen in 73.5% of the subjects. If we observe only patients with urolithiasis, we find that 50% of the cases present hepatic steatosis, which indicates that there is a shared causal relationship between the 2 pathologies.

In observational studies that evaluated the nutritional and metabolic characteristics associated with these pathologies, the causal mechanism is not yet known; however, the production of free radicals of oxygen and the lipid peroxidation or hepatocyte mitochondrial damage are important factors for the genesis of the stones. An increase in the systemic production of free radicals of oxygen at the renal level and mitochondrial lipid peroxidation causes an increase in the concentration of calcium oxalate, favoring its precipitation and formation of stones (11, 12), findings that have been supported in the Carrasco-Valiente (13) study.

It has also been reported that fatty acids can modify the urinary excretion of calcium and oxalate within the phosphorylation of arachidonic acid in association with nephrolithiasis. This is because the phosphorylation of arachidonic acid determines a cascade of metabolic effects on calcium homeostasis, which generates hypercalciuria owing to the action of secondary messengers or the PGE2/vitamin D receptor (14).

The study of Kim S et al. (3) observed that the association between NAFLD and nephrolithiasis was more prominent in participants younger than 50 years of age (adjusted HR, 1.19; 95% CI, 1.14 ± 1.24) than in those older than 50 years (adjusted HR, 1.06; 95%CI, 0.95 ± 1.19) ($P < .001$). We found similar findings when the distribution by age range was made. We observed that the simultaneous association between hepatic steatosis and urolithiasis decreases significantly and inversely with age.

Different studies have evaluated the simultaneous presentation of dyslipidemia and urolithiasis taking into account that a metabolic alteration is one of the most important causes of fatty liver. Although the causal factor has not been determined yet, a common path must exist given its high association. Other studies also support this idea like Torricelli's study (15). This study reported on 2442 patients and was based on the multifactorial origin of urolithiasis, in which it was found that patients with high levels of total cholesterol and triglycerides presented urolithiasis more frequently than normal controls ($P = .006$ and $P < .0001$, respectively), finding with statistical significance that these patients had higher serum concentrations of calcium oxalate and uric acid. Ding Q et al. (16) performed a case–control study and found that patients with hypertriglyceridemia and low high-density lipoprotein cholesterol levels had an increased risk of nephrolithiasis (OR, 1.31; 95% CI: 1,01 ± 1,71; OR 7,57). The study of Kang (17) calculated the risk of recurrence of urolithiasis to be up to 50% at 5 years in patients with dyslipidemia and metabolic syndrome. They followed up 1561 patients and identified a relationship between dyslipidemia and urolithiasis, with patients with high levels of triglycerides being at a higher risk for recurrence of urolithiasis (95% CI, 1.2–2.8; $P = .005$)–a statistically significant result and an independent risk factor. Masterson et al. (18) evaluated the diagnosis of dyslipidemia and urolithiasis in 52 184 patients and confirmed an association of these pathologies, thus suggesting that low levels of high-density lipoprotein cholesterol predispose to the presence of nephrolithiasis (HR, 1.4; 95%CI, 1.1–1.7; $P = .003$)–a statistically significant result compared with other reports where other components of the lipid panel favor the formation of urinary stones. Thus, treating dyslipidemia could mitigate the risk of urolithiasis.

Observational studies such as those of Paten (19) (98 patients), Cho (20) (712 patients), and Naya et al. (21) assessed patients diagnosed with metabolic syndrome and insulin resistance, and evaluated its effect on the development of urolithiasis, observing that these pathologies cause changes that favor ammoniagenesis and systemic acidosis, increase calcium bone resorption, and decrease hypercalciuria. The reabsorption of citrates causes hypocitraturia and favors the precipitation of

Table 2. Severity of Fatty Liver Disease and Urolithiasis

Fatty Liver Degree	Without Urolithiasis	Urolithiasis	Overall
Absence	213 (38.5%)	339 (61.4%)	552 (100%)
Mild-to-Moderate	65 (28.6%)	162 (71%)	227 (100%)
Moderate-to-Severe	56 (24.2%)	175 (75.7%)	231 (100%)

$P < .0001$.

calcium in urine. In acid urine, the low pH increases the precipitation of uric acid, which is favored by high serum levels secondary to the increase in intake of protein that chemically predispose to stone formation (4, 22).

The limitations of our study lie in its retrospective type and in the lack of the clinical, nutritional, and anthropometric information, as well as the associated pathologies, treatments, and lifestyle, of the subjects assessed that may favor the genesis of these pathologies. A study taking these factors in consideration is recommended to determinate the cause of the relationship between the 2 conditions more accurately. A follow-up study is necessary to evaluate the natural evolution of the disease and to search why the associations between hepatic steatosis and urolithiasis decrease with age, as they are inferred to be due to changes in lifestyle that favor the decrease or regression of liver and kidney disease.

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