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Can we predict the co-occurrence of nonalcoholic fatty liver disease and uric acid urolithiasis? Assessment of prevalence based on findings in preoperative computed tomography imaging

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ABSTRACT

Introduction: Observational studies have already shown an association between the co-occurrence of nonalcoholic fatty liver disease (NAFLD) and urinary tract stones. A plausible mechanism for their development is the increased consumption of high-fat foods and fructose syrup, which if consumed in excess, is metabolized to uric acid. Its excessive concentration in the urine lead to the development of urolithiasis. Therefore, it can be assumed that NAFLD will most often co-occur with uric acid stones. Hence, we aimed to evaluate the co-occurrence of both diseases based on findings in preoperative computed tomography (CT) imaging.

Materials and methods: The study population included all consecutive patients with urinary tract stones who underwent surgical treatment between 2019–2022. A total of 228 patients were enrolled in this study and evaluated for the presence of strict exclusion criteria. After applying the exclusion criteria 124 patients undergoing surgical treatment of urolithiasis were included in the further analysis.

Results: Uric acid deposits defined as stones with a density <500 HU were found in 12.90% of patients. Nonalcoholic fatty liver disease was diagnosed in 28 patients, as many as 42.86% of whom were diagnosed with uric acid stones ($p < 0.001$). A significant correlation was found between the incidence of both disease entities at 0.483 (Q-Yule coefficient).

Conclusions: The presence of NAFLD in imaging studies is more often found in patients with uric acid stones. Therefore, diagnosis of co-occurrence of both conditions might allow the implementation of appropriate treatment without the need for chemical analysis of the deposit.

Keywords: nonalcoholic fatty liver disease; NAFLD; urolithiasis; urinary stone disease; uric acid stones; computed tomography imaging; metabolic syndrome.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of conditions that vary from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, which is at high risk of progressing to hepatocellular carcinoma. Nonalcoholic fatty liver disease is defined as a condition where more than 5% of non-diseased hepatic cells contain fatty deposits without a history of alcohol consumption [1, 2]. Epidemiological studies show that the global prevalence of the disease is rapidly rising now concerning approx. 25% of the general population [1, 3]. Nonalcoholic fatty liver disease is considered to be driven by various metabolic disorders including obesity, diabetes, insulin resistance, dyslipidemia, and hyperuricemia. In fact, some scientists often refer NAFLD to as the "hepatic manifestation" of metabolic syndrome. Recently, there is growing evidence that fatty liver disease may be a key driver in metabolic syndrome [4]. Moreover, hepatic involvement could be just 1 component of a multi-organ syndrome that involves the cardiovascular, renal, and endocrine systems [5, 6].

Various studies indicate that NAFLD is also linked with the risk of developing urolithiasis [1, 2]. Kidney stone disease is one of the most common acute urological conditions with a globally increasing prevalence between 5–15% in various regions [7]. The etiology includes genetic, ethnic, geographical, climatic, and dietary factors. The increase in urolithiasis incidence might be associated with an increase in obesity and diabetes mellitus, consumption of diets rich in salt, animal protein, sucrose, sugar-sweetened beverages, and global warming [7, 8]. The co-incidence of NAFLD and urolithiasis suggests that there must be a common pathology and mechanisms leading to the development of both diseases, especially the presence of shared metabolic disorders. One of the plausible explanations is an increase in the consumption of fatty foods and fructose syrup, which is widely used in the food industry. The addition of liquid fructose to dietary saturated fatty acids is determinant in liver steatosis and hypertriglyceridemia production. Moreover, fructose is one of the substrates for the endogenous synthesis of uric acid [9]. A significant increase in serum uric acid levels might eventually lead to the development of uric acid calculi. Hence, the purpose of this study was to identify the relationship between uric acid lithiasis and NAFLD and assess the co-occurrence of those 2 diseases based on findings in preoperative computed tomography (CT) imaging.

MATERIALS AND METHODS

Ethical approval and study conception

This single-center, retrospective study was exempt from further review by the Institutional Review Board (Bioethical Committee) of the Pomeranian Medical University in Szczecin (PMU), Poland, due to the nature of the study (protocol number KB.006.13.2023, date of approval 19/01/2023) and was conducted according to the regulations set forth by the Declaration of Helsinki. Written and informed consent for research participation was routinely obtained from all patients involved in this study for the use of their anonymized medical data collected during hospitalization.

The study conception was based on the assumptions presented by Badillo et al. who tried to identify a relationship between urolithiasis and fatty liver disease by examining for common factors that could be used to reduce their incidence and complications. The researchers evaluated abdominal CT scans performed in a population consisting of individuals of age >18 years [10]. We decided to conduct a similar study with the use of preoperative CT imaging and protocols for CT urinary tract and abdominal presented in the abovementioned research.

Study population

At first, we included in the study population all consecutive patients with urinary stone disease who underwent surgical treatment between 2019–2022 in the Department of Urology and Urological Oncology PMU. A total of 228 patients were enrolled in this study and evaluated for the presence of strict exclusion criteria which included:

- splenectomy in the past;
- hepatosplenomegaly;
- a history of liver or kidney transplant;
- other liver diseases including viral hepatitis, liver cirrhosis, hepatocellular carcinoma, metastasis from other primary cancer;
- malformations of the urinary tract;
- current dialytic therapy;
- urinary tract infection;
- pregnancy;
- alcoholic disease;
- suboptimal image quality of CT examination due to beam hardening artifact or respiration artifact;
- lack of non-contrast CT imaging.

After applying the aforementioned exclusion criteria, only 124 patients were eventually included for further analysis. For each patient, we collected the following data from medical records such as age, gender, mode of hospital admission (planned or emergency admission), and length of stay. Additionally, preoperative CT scans of the abdomen and pelvis without contrast enhancement were reviewed in each patient to assess NAFLD and urolithiasis prevalence. Every CT assessed in this study was performed at PMU with the same protocol using a slice thickness of 1.5 mm. Precise protocols used for the assessment of CT were as described below.

Protocol for the assessment of NAFLD prevalence

Based on protocols described by other researchers, we determined liver density using a circular region of interest (ROI) parameter of 3.14 cm^2 in area. Isolated measurements of left, right, caudate, and quadrate lobes were made. An average of the value obtained in each hepatic lobe was done for a final single value of the mean liver density. Spleen density was obtained by averaging 3 measurements with the use of a 3.14 cm^2 area circular ROI at the upper, middle, and lower segments.

Eventually, NAFLD was diagnosed when there was a difference in the liver-spleen density ≤5 Hounsfield units (HU). Additionally, we assessed the severity of fatty liver disease and distinguished 2 groups from the study population: mild-to-moderate steatosis if results in the liver-spleen density were between 5 HU and –10 HU, and moderate-to-severe steatosis for results lower than –10 HU. Results >5 HU were considered as a lack of steatosis [10].

Protocol for the assessment of urolithiasis prevalence

In every patient included in the study CT examination was performed before planned surgical treatment to verify the presence of kidney stones disease. We additionally evaluated the following parameters:

- mean CT attenuation value of calculi (HU);
- size of the calculi in its largest dimension (mm);
- location of the stones in the urinary tract (kidneys, ureters, or the bladder);
- presence of hydronephrosis;
- multitude of the stones (single or multiple);

Stone density was determined using a circular ROI that occupied the largest diameter of the stone surface. The mean CT attenuation value of deposits <500 HU was taken as the criterion for the presence of uric acid lithiasis [10, 11, 12]. Calculi with density ≥500 HU were classified as a different type of lithiasis.

STATISTICAL ANALYSIS

Before conducting statistical analysis, obtained data were checked by 2 independent reviewers for internal consistency and correctness of the exclusion criteria applied. Descriptive statistics included mean and standard deviation for normally distributed data. Qualitative data were presented as numbers. Single variables were compared using an independent χ^2 test for non-parametric variables. The association between NAFLD and uric acid urolithiasis was assessed using the Yule coefficient of association (Yule's Q). We considered p-value <0.05 as statistically significant. All tests conducted during statistical analysis were performed using Stat-Soft statistical software, version 13.5 (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

Among 228 patients with urinary tract stones undergoing surgical treatment that were recruited to this study, 104 were excluded due to the presence of exclusion criteria. Hence, 124 patients eventually constituted the study population. The mean age of the patients from the study group was 54.13 ±15.81 years. Women accounted for nearly 55%, and men for about 45% of the analyzed population. Length of stay deviated between 2–17 days, with a mean duration of 4.48 ±2.08 days. The general characteristics of the study population was presented in Table 1.

TABLE 1. General characteristics of the study population

Variables	Study population (n = 124)	% of the study population
Age, years		
Mean	54.13	–
SD	15.81	–
Gender		
Female	68	54.84
Male	56	45.16
Mode of hospital admission		
Planned admission	118	95.16
Emergency admission	6	4.84
Length of stay, days		
Mean	4.48	–
SD	2.08	–
NAFLD on CT imaging		
No	96	77.42
Yes	28	22.58

SD – standard deviation; NAFLD – nonalcoholic fatty liver disease; CT – computed tomography

In this study, we analyzed 124 CT scans performed before the planned surgical treatment of urinary tract stones between 2019–2022. We did not analyze the type of the performed surgical procedure, nor its duration. General characteristics of urinary tract stones among the study population are presented in Table 2. The mean diameter of the deposits was 22.71 mm. Multiple deposits in the urinary tract appeared more often than single deposits (62.90% vs. 37.10%, respectively). The stones were located in the kidneys in most cases (n = 108; 87.10%).

In only 16 cases the deposits had mean attenuation <500 HU. Therefore they were considered as deposits consisting of uric acid, which accounted for 12.90% of all cases of urolithiasis among patients in the study population. Uric acid lithiasis was present in 11.76% of women and 14.29% of men. However, there were no significant differences in the incidence of uric acid stones between the genders (p = 0.677) – Table 3.

Based on the analyses of preoperative CT images, we found 28 cases of NAFLD. This represented 22.58% of the study population. Moreover, among all of the NAFLD cases diagnosed, 12 subjects were patients with co-occurrence of uric acid stones. Therefore, as many as 42.86% of patients with NAFLD were also diagnosed with uric acid stones (p < 0.001). Based on the statistical analyses, we find a significant correlation between the co-occurrence of both disease entities at 0.483 (Q-Yule coefficient). Additionally, we assessed the severity of fatty liver disease and distinguished 2 groups from the study population: mild-to-moderate steatosis and moderate-to-severe steatosis (Tab. 4).

TABLE 2. General characteristics of urinary tract calculi among the study population

Variables	Study population (n = 124)	% of the study population
Hydronephrosis		
No	79	77.06
Yes	45	22.94
No. of stones		
Single	46	37.10
Multiple	78	62.90
Diameter of calculi, mm		
Mean	22.71	–
SD	13.33	–
Location of calculi		
Kidney	108	87.10
Ureter	13	10.48
Bladder	3	2.42
Mean CT attenuation value of calculi, HU		
<500	16	12.90
≥500	108	87.10

SD – standard deviation; CT – computed tomography; HU – Hounsfield units

TABLE 3. Comparison of the group with uric acid stones and the group with other types of lithiasis

Variables	Population with uric acid stones (n = 16)	Population with a different type of lithiasis (n = 108)	p-value
Gender			
Female	8 (11.76%)	60 (88%)	0.677
Male	8 (14.29%)	48 (86%)	
NAFLD			
No	4	92	<0.001
Yes	12	16	

NAFLD – nonalcoholic fatty liver disease

TABLE 4. The severity of fatty liver disease

Severity of steatosis	Population with NAFLD (n = 28)	% of the population with NAFLD
Mild-to-moderate steatosis	18	64.29
Moderate-to-severe steatosis	10	35.71

NAFLD – nonalcoholic fatty liver disease

DISCUSSION

It has already been described by other researchers that NAFLD not only contributes to liver-related morbidity and mortality but also affects multiple organs causing extra-hepatic comorbidities. Additional extra-hepatic manifestations of NAFLD include type 2 diabetes mellitus, cardiovascular disease, obstructive sleep apnea, chronic kidney disease, osteoporosis, and polycystic ovarian syndrome [4]. The golden standard for diagnosis of NAFLD is liver biopsy. Nevertheless, this is an invasive procedure and can be fraught with complications [10]. Hence, noninvasive tests, especially imaging techniques, should be taken into account in clinical practice when diagnosing NAFLD [13]. Liver steatosis can be identified by CT imaging. However, it is not routinely performed in order to screen for NAFLD due to concerns about radiation exposure [14]. Meta-analysis presented by Bohte et al. revealed that CT detects steatosis with a sensitivity of 46.1–72.0% and specificity of 88.1–94.6% [13]. It is worth noting that CT is often performed for other clinical indications. Thus, screening for NAFLD, especially for scientific purposes, could be possible whenever a patient has an abdominal CT scan performed. Therefore, inspired by other researchers, we decided to investigate the presence of NAFLD in patients with urolithiasis in our Urology Department who have routinely performed CT imaging before planned surgical treatment for urinary stones.

Urolithiasis is one of the most common urological conditions with still increasing prevalence worldwide [15, 16, 17]. The association between NAFLD and urinary stones disease has been extensively researched in recent years and has already been described in multiple studies. Qin et al. conducted one of the biggest meta-analyses concerning this issue that included a total of 7 observational studies with 226,541 individuals (24.7% with NAFLD) and 19,184 urolithiasis (8.5%). Reported data provided evidence suggesting that patients with NAFLD are at a 1.73 fold increased risk of urolithiasis than those without NAFLD [18]. Another research conducted by Einollahi et al. revealed a higher detection frequency of stone formation in patients with NAFLD (OR 2.4; 95%CI 2.1–2.7; $p < 0.0001$). Moreover, NAFLD seemed to be an independent risk factor for urolithiasis [19]. However, the etiopathogenesis underlying these comorbidities remains unclear and not completely defined [4]. Nevertheless, the co-incidence of NAFLD and urolithiasis indicates that there must be a common pathology and mechanisms leading to the development of both diseases. One of the plausible explanations for this increase in risk is the presence of shared metabolic disorders, such as diabetes mellitus, hypertension, obesity, and metabolic syndrome in patients with NAFLD and urinary stone disease, which are known as significant factors leading to the development of both diseases [20, 21, 22]. Most available studies additionally implicate the prominent role of reactive oxygen species (ROS) and oxidative stress (OS) in the pathogenesis of both NAFLD and stone formation in the urinary tract [4, 18, 19]. Morita et al. reported in their study that free radicals as well as a diet rich in fat induce the accumulation of fat in the liver by mechanisms with concomitant involvement of lipid peroxidation [23]. This assumption is supported by results presented by Wang et al. In their review, they stated that defects in mitochondrial β-oxidation, enhanced fatty acid synthesis, and impaired secretion of triacylglyceride (TG)-rich very low-density lipoproteins also contribute to hepatic steatosis, as well as accumulation of ROS that oxidize fat deposits to form lipid peroxidation products, which lead to steatohepatitis, necrosis, inflammation, and fibrosis [24].

So far, there is no available research that would analyze the association between NAFLD and urinary stones specifically composed of uric acid. However, there are multiple studies on the pathophysiology of both disorders which encouraged us to look for a correlation between NAFLD and this type of urolithiasis. Jensen et al. presented a review of recent clinical and experimental evidence that fructose appears to have a major role in inducing fat accumulation in the liver, due to both increased lipogenesis *de novo* and impaired fat oxidation, contributing to the increased risk of NAFLD development [25]. On the other hand, the excessive consumption of fructose, naturally present in honey and fruits, but commonly used especially in sugary sweetened beverages, has been considered an important inducer of hyperuricemia. Serum uric acid levels are controlled through the balance between urate synthesis and excretion. Multiple exogenous and endogenous factors can impair this balance, inducing hyperuricemia. One of the most important inducers of hyperuricemia is excessive consumption of fructose. Uric acid is removed from the bloodstream through renal (70%) and biliary (30%) systems [26]. The increased uric acid level in the urine can lead to the development of uric acid calculi. Therefore, similar metabolic pathologies that lay upon the development of fatty liver and uric acid calculi indicate, that this type of urolithiasis specifically should be more often associated with NAFLD. The results presented in our study prove that this assumption might be correct. Based on the preoperative CT scans performed routinely in every patient with urolithiasis before planned operative treatment, we diagnosed NAFLD in 28 subjects, of whom up to 42.86% were diagnosed with uric acid stones ($n = 12$; $p < 0.001$). Additionally, we found a significant correlation between the incidence of both diseases at 0.483 (Yule's Q). Nevertheless, this result should be further investigated in a larger study group.

Uric acid stones account for 8–10% of all kidney stones in the United States and up to 40% of all stone cases globally with higher prevalence in the Middle East and some parts of Europe [27, 28]. Researchers report that 79% of uric acid stones occur in men, mostly between 60 and 65 years old [29]. Uric acid calculi defined as stones with a density <500 HU were found in 12.90% of all cases of urolithiasis among patients in our study population (11.76% of females vs. 14.29% of males). Nevertheless, there were no statistically significant differences between genders regarding uric acid lithiasis occurrence ($p = 0.677$).

Despite finding previously unresearched and statistically significant correlations between NAFLD and the development of uric acid stones, our study had several limitations. First of all, this single-center study had restrictions regarding the size of the study group. Once the strict exclusion criteria have been applied, our study population consisted of only 124 out of 228 participants primarily included in the study. Therefore, further investigation in other academic centers on larger sample sizes would enable a more profound analysis of the association presented in our research and more reliable conclusions. Secondly, our study was limited by constraints inherent to the retrospective nature of the data analysis. Hence, screening for fatty liver was restricted only to preoperative CT scans. Therefore, we were unable to verify by the use of other diagnostic techniques if the patients had NAFLD indeed. Thirdly, the measurements needed to assess the CT scans were performed by researchers who are not radiology specialists but have received adequate training in CT assessment for the evaluation of the pathologies examined in the presented study. Therefore, there is a slight risk that there may have been some minor errors in the measurements performed. However, as the same 2 researchers always supervised the CT assessment by other investigators, measurement errors were kept to a minimum and should not affect the results obtained.

CONCLUSIONS

Nonalcoholic fatty liver disease is significantly more common in patients with uric acid stones. The non-invasive diagnosis of NAFLD on preoperative CT imaging in patients diagnosed with urolithiasis may be an important predictor of stone composition. Thus, allowing appropriate treatment to be implemented without the need for biochemical analysis of the deposit after performed operative urolithiasis treatment. However, further investigation is required to fully explore the co-occurrence of fatty liver and uric acid calculi and their pathomechanisms.

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