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Association of nonalcoholic fatty liver disease (NAFLD) with urolithiasis

[1]Einollahi B, [2]Naghii MR, [3]Sepandi M

[1]Nephrology and Urology Research Center, [2]Sport Physiology Research Center and Department of Nutrition, Health School, and [3]Department of Epidemiology and Statistics, Health School, Baqiyatallah (a.s.) University of Medical Sciences, Tehran, Iran
E-mail: naghiimr@yahoo.com

Objective. The NAFLD is related to metabolic disorders and is negatively associated with kidney function. Renal stone disease (urolithiasis) is an increasing form of a common renal disease that is a multifactorial disorder influenced by both intrinsic and extrinsic, mainly environmental factors. The association between the fatty liver and renal calculi, as a specific underlying risk factor, has received no attention, so far. Therefore, in this study, a possible relationship between fatty liver with renal calculi and urolithiasis is investigated.

Methods. In a cross sectional study, a total of 11245 ultrasonography reports revealing the condition of fatty liver, kidney stones (urolithiasis), or a combination of both of them, were categorized and evaluated statistically. Descriptive statistics determined the number (frequency & percentage) of each condition. The statistical significance of the association between fatty liver and kidney stone, and vice versa, was evaluated using McNemar's test. The Chi Square Test assessed the relationship between genders. Odds ratios and 95% confidence intervals (95% CI) assessed the likelihood of characteristics of urolithiasis for fatty liver patients.

Results. We found 8% frequency of urolithiasis among subjects with healthy liver. NAFLD was identified in 30%, while urolithiasis in 11% subjects from all individuals studied. The present study diagnosed urolithiasis in 17% of patients with fatty liver. Its occurrence was more common in men than women. Data revealed more common diagnosis of fatty liver (48%) in patients with urolithiasis, which was also higher in males than females. The higher NAFLD was linked with urolithiasis, indicating a greater chance of their association. Interestingly, the detection frequency of urolithiasis in the patients with NAFLD was also markedly higher (odds ratio: 2.4, 95% CI 2.1-2.7). The NAFLD appears to be an independent variable as a risk factor for stone formation.

Conclusions. 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 the onset of the urolithiasis. It is suggested that lipid peroxidation, oxidative stress and changes in the urinary constituents in the NAFLD may be considered as a risk factor in the progression of stone formations.

Key words: nonalcoholic fatty liver disease, urolithiasis, association

Nonalcoholic fatty liver disease (NAFLD) has been reported to be related to metabolic disorders frequently accompanied by an abnormal liver function. Now it is considered to be a hepatic representative of the metabolic syndrome (MetS) (Hamaguchi et al. 2012). The NAFLD is a rapidly emerging chronic liver disorder that affects

Corresponding author: Mohammad Reza Naghii, PhD., Sport Physiology Research Center and Department of Nutrition, Health School, Baqiyatallah (a.s.) University of Medical Sciences, Tehran, Iran; e-mail: naghiimr@yahoo.com.

up to the third of the human population worldwide, and is a marker of pathological ectopic fat accumulation combined with a low-grade chronic inflammatory state. This results in several deleterious pathophysiological processes, including abnormal glucose, fatty acid, and lipoprotein metabolism, increased OS, deranged adipokine profile, hypercoagulability, endothelial dysfunction, and accelerated progression of the atherosclerosis (Bhatia et al. 2012). It has been linked to an increased cardiovascular morbidity (Mantovani et al. 2012; Tarnoki et al. 2012) associated with MetS, insulin resistance (IR) (El-Koofy et al. 2012), and a higher risk of osteoporosis in postmenopausal women (Moon et al. 2012). The high prevalence of non-alcoholic steatohepatitis (NASH), i.e. a more progressive form of NAFLD in patients with gallbladder stone, is currently reported with the typical risk factors for both diseases (Yener et al. 2010).

Recent findings indicate that NAFLD is negatively associated with kidney function and NAFLD and mild kidney function damage (MKFD) may share similar risk factors and/or pathological processes (Li et al. 2012). It is also associated with a higher prevalence of chronic kidney disease in patients with the type 1 diabetes (Targher et al. 2012), and changes in renal function are reported in morbid obese patients with NAFLD (Machado et al. 2012). Urolithiasis is an increasing form of common renal disease that is associated with crystal deposition in the renal medulla and urinary tract. It is a multifactorial disorder influenced by both intrinsic and extrinsic, mainly environmental factors (Evan 2010). Current epidemiological studies have revealed an association of obesity, diabetes mellitus, hypertension, and MetS with kidney stone disease. These results indicate that MetS causes changes in urinary constituents, leading to an increased risk of both uric acid and calcium oxalate (CaOx) stone formations. Thus kidney stone disease should be considered as a component of the MetS (Kohjimoto et al. 2011).

Recently, in our routine clinical practice, we noticed a concomitant diagnosis of both fatty liver and urolithiasis, coincidentally found in two patients who underwent an abdominal ultrasonography as a routine medical examination. It is known that abdominal sonography seems to be a useful tool in detecting hidden intraabdominal pathologies such as fatty liver and mass, abnormal findings in the kidney, bladder, and gallbladder in patients with spinal cord injury (Shin et al. 2006). The association between fatty liver and renal calculi or urolithiasis, as an underlying risk factor, has received no attention, so far. Literature reviews using Medline/PubMed articles revealed no data or studies on this association and there are no reports available, until date concerning the involvement of fatty liver in the pathogenesis and progression of nephrolithiasis. Therefore, we have decided to investigate the probable relationship between fatty liver with renal calculi (urolithiasis) in patients who underwent abdominal ultrasonography examination.

Materials and Methods

In a cross sectional study, a total of 11245 ultrasonography reports examining the condition of fatty liver, kidney stones (urolithiasis), or their combination in subjects referred for sonographic evaluations, obtained from Office of Medical Records, Baqiyattallah-alazam Hospital, Baqiyattallah University of Medical Sciences, were used. The sonographic evaluations of the livers and kidneys were performed by the attending expert radiologists in the Department of Radiology and Sonography who were blinded to the clinical evaluations or the aim of this study at the time of examinations. The diagnosis and detection of fatty liver disease, renal lithiasis/urolithiasis, or both complications were determined by the radiologists registered. The severity of fatty liver was scored, reported, and analyzed statistically. Descriptive statistics were used according to the type of variable evaluated to determine the number (frequency and percentage) of each condition. The statistical significance of the association between fatty liver and kidney stone and vice versa was evaluated using McNemar's test. The Chi Square Test was also used to assess the relationship between gender with fatty liver and kidney stones. Odds ratios and 95% CI were calculated to assess the likelihood of characteristics of urolithiasis for fatty liver patients. The level of statistical significance was 0.05. The statistical analysis was performed with a Statistical Package for the Social Sciences [(SPSS 17.0), New York: McGraw-Hill].

Results

The population studied included the retrieved records of 11245 individuals. The ultrasound findings (Table 1) showed that 7284 individuals (65% of total number) were healthy (no fatty liver, no urolithiasis). It was found that 7904 (70%) of subjects were free of fatty liver condition or disease and had a normal liver echopattern. The frequency of urolithiasis (n=620) among them was 8%. In contrast, 3341 (30%) cases of fatty liver patients and 1193 (11%) cases of urolithiasis were identified in all individuals.

Expressing the data (Table 1) according to gender, 5698 males (51%) and 5547 females (49%) were evalu-

ated. There were 1778 (31%) male and 1563 (28%) female cases of fatty liver and 650 (11%) male and 543 (10%) female cases of urolithiasis. In the males, the frequency of urolithiasis (n=335) within total male fatty liver patients (n=1778) was 19%, while in the female patients the frequency of urolithiasis (n=238) within total female fatty liver patients (n=1563) was 15%, (p=0.006). Meanwhile, in the males, the frequency of urolithiasis (n=315) among the subjects with normal fatty liver (n=3920) was 8%, while in the females the frequency of urolithiasis (n=305) among the subjects with normal fatty liver (n=3984) was 7%, (p=0.54).

For fatty liver patients, detection or diagnosis of fatty liver was associated with a higher risk of developing urolithiasis (p<0.0001), (odds ratio: 2.4, 95% CI 2.1-2.7) (p<0.0001). This significant association in males and females was found to be 2.6 [2.2-3.1], and 2.1 [1.8-2.5], respectively; p<0.0001 and p<0.0001). Moreover, significant associations between gender with fatty liver (p<0.0001) and between gender with urolithiasis (p<0.005) were observed, while the odds ratio for female gender in fatty liver patients and in urolithiasis patients appeared to be 0.86 [0.79-0.93], and 0.84 [0.74-0.95], respectively (p<0.0001 and p<0.005).

The frequency of urolithiasis (n=573) among total fatty liver patients (n=3341) was 17%, with a frequency of 19% and 15.3% in males and females, respectively (p=0.006) (Table 2).

The frequency of fatty liver (n=573) among the kidney stone patients (n=1193) was 48%, with a frequency of 51% and 44% in males and females, respectively (p=0.008) (Table 3).

Table 1

Absolute and relative frequencies of fatty liver cases, kidney stone cases, fatty liver + kidney stone cases, and normal subjects observed in a total of 11245 (M=5698 [51%], F= 5547 [49%]) by ultrasound parallely in liver and kidney

Diagnosis	Total No. (%) (n=11245)	Male No. (%) (n=5698)	Female No. (%) (n=5547)	Ratio M:F
Fatty liver	2768 (25%)	1443 (25%)	1325 (24%)	~ 1:1
Kidney stone	620 (5.5%)	315 (5.5%)	305 (5.5%)	~ 1:1
Fatty liver + Kidney stone	573 (5.0%)	335 (6%)	238 (4%)	1.4:1
Total fatty liver	2768+573=3341 (30%)	1443+335=1778 (31%)	1325+238=1563 (28%)	~ 1:1
Total kidney stone	620+573=1193 (11%)	315+335= 650 (12%)	305+238=543 (10%)	1.2:1
Normal subjects	7284 (65%)	3605 (63%)	3679 (66%)	~ 1:1

No. – absolute frequency (number), % – relative frequency, M – males, F – females, Normal Subjects – no fatty liver, no kidney stone

Table 2

Total number and gender frequency of kidney stones in fatty liver patients

Fatty liver Patients (total number)	Kidney stones among fatty liver patients (M/F) (number and %)	Kidney stones among male fatty liver patients (number and %)	Kidney stones among female fatty liver patients (number and %)
3341	573 (17%)	335 (19%)	238 (15%)

Note: The frequency of kidney stones among fatty liver patients is 17%.

Table 3

Total number and gender frequency of fatty liver in kidney stone patients

Kidney stones patients (total number)	Fatty liver among kidney stones patients (M/F) (number and %)	Fatty liver among male kidney stones patients (number and %)	Fatty liver among female kidney stones patients (number and %)
1193	573 (48%)	335 (51%)	238 (44%)

Note: The frequency of fatty liver among kidney stones patients is 48%.

Discussion

The NAFLD is considered to be one of the most common liver diseases in the world characterized by the accumulation of liver fat without alcohol consumption and is characteristic for the majority of asymptomatic patients. Its diagnosis is based on imaging methods confirmed by histopathology of liver biopsy, if required (Paredes et al. 2012). It is estimated that NAFLD afflicts ~ 20-30% of the general population and over 70% of patients with type 2 diabetes mellitus (DM2) with problems far beyond the liver (Targher et al. 2011). NAFLD is closely related to conditions of IR such are DM2, obesity, and dyslipidemia (Bellentani and Marino 2009), as well as cardiometabolic risk factors (Bhatia et al. 2012) and kidney function (Li et al. 2012; Machado et al. 2012; Targher et al. 2012). NAFLD is also associated with an increased chronic kidney disease risk in nondiabetic and nonhypertensive Korean men, irrespective of MetS (Chang et al. 2008). Chronic kidney disease is also known to be present in Japanese patients with NAFLD. Its annual incidence moves around 1.2% (Arase et al. 2011).

However, the association between NAFLD and urolithiasis, as a specific underlying risk factor, has received no attention, so far. In our study, we found 8% urolithiasis frequency in subjects with healthy liver. NAFLD was identified in 30% while urolithiasis in 11% of subjects investigated. The present study diagnosed urolithiasis in 17% of patients with the fatty liver. It was more common in men than women (with a frequency of 19% of males and 15% of females, respectively (p=0.006). Other interesting data revealed the more common diagnosis of fatty liver in 48% of patients with urolithiasis, which was also higher in males (51%) in comparison with females (44%) (p=0.008).

It is worth to note that higher NAFLD is linked with urolithiasis, indicating a greater chance of their association. Interestingly, the detection frequency of urolithiasis in patients with NAFLD was also markedly higher (odds ratio: 2.4, 95% CI 2.1-2.7) and NAFLD appears to be an independent variable as a risk factor for stone formation.

Awareness of the association between NAFL and urolithiasis may indicate for some common risks and pathogenic factors. OS has been implicated in the pathogenesis of NAFLD, but the exact nature of active species and the underlying mechanisms have not been elucidated yet. It is proposed that free radicals as well as high-fat diet induce fatty liver by similar mechanisms, in which lipid peroxidation may be involved (Morita et al. 2012). In the liver itself, because of the alteration to lipid metabolism a condition referred as lipotoxicity, fatty acids undergo extra-mitochondrial (abnormal) oxidation, leading to OS (Aller et al. 2008, 2009). The release of reactive particles of oxygen generated in OS may increase mitochondrial damage in hepatocytes and expand extra-mitochondrial oxidation of fatty acids (Neuschwander-Tetri and Caldwell 2003).

According to several observations oxidative and systemic metabolisms are compatible with stone formation (Schwille et al. 2009). The kidney is an organ highly vulnerable to damage by reactive oxygen species (ROS), likely due to the abundance of long-chain polyunsaturated fatty acids in the composition of renal lipids. Most clinical and experimental studies have shown that OS is increased in kidney and systemic circulation and OS has a critical role in the pathophysiology of several kidney diseases, and many complications of these diseases are mediated by OS, OS-related mediators, and inflammation. Chronic blockade of OS with antioxidant improves OS in kidney. Antioxidant and reactive oxygen scavengers have been shown to be effective in animals in protecting kidney (Ozbek 2012). There is a possible role of lipid peroxidation in CaOx stone formation which may have a relationship with the major risk factors in urine including oxalate, calcium, phosphorus and MDA (Ghalayini et al. 2011). Patients undergoing urolithiasis showed an elevation of acute phase markers, associated with OS as expressed by an increase in lipid peroxidation products and decrease in the antioxidant enzyme activity (Carrasco-Valiente et al. 2012).

Data of several studies have revealed protective or an inhibitory role for antioxidants against urinary stone formation. The cell is endowed with several antioxidant systems to limit the extent of the lipid peroxidation. The adverse cytotoxic effects of CaOx monohydrate (COM) presumably attributed to OS, as indicated by lipid peroxidation assay, were completely prevented with N-acetylcysteine (NAC), a potent antioxidant (Davalos et al. 2010). In rats, vitamin E treatment completely prevented CaOx crystal deposition in the kidney, by preventing hyperoxaluria-induced lipid peroxidation and tissue antioxidant imbalance (Thamilselvan and Menon 2005). Another study shows that low vitamin E disrupts the redox balance and causes cell death, thereby favoring crystal formation (Huang et al. 2009). To evaluate the association between serum antioxidant levels and self-reported prevalence of urolithiasis, it has been reported that lower levels of alpha-carotene, beta-carotene, and

beta-cryptoxanthin are associated with a history of kidney stones and indicate the highest levels of these antioxidants may be protective against the formation of kidney stones (Holoch and Tracy 2011). The mechanism underlying the link between the two disorders may possibly be mediated through lipid peroxidation and lack of antioxidant capacity for association of the described diseases. The diagnosis of urolithiasis in patients with fatty liver may justify routine assessment of OS (analyzing antioxidant systems and lipid peroxidation markers or products) to establish a link between these two conditions. Further data indicate that fatty liver may cause changes in urinary constituents, leading to an increased risk of stone formation. Despite the fact that liver fat or the presence of fatty liver was found to be closely associated with nephrolithiasis, no study, as far as we know, has been conducted to investigate specifically the relevance of fatty liver to stone formation. Thus, our study may provide new insights into this issue.

Conclusion

These primary findings underscore the possible clinical relevance of NAFLD with urolithiasis and the importance of an earlier assessment in the process of diagnosis in patients at risk. The present finding suggests that performing routine kidney and urinary system examination during ultrasonography for fatty liver identification may be justified given the moderate prevalence of urolithiasis in fatty liver patients; otherwise, a few number of urolithiasis patients could go undiagnosed for a long time. Data and conclusions presented here should be considered to be preliminary and we merely note an association that merits further investigation.

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