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Specific Effects of Some Metabolic Syndrome Components on Kidney Stone Formation: A Multicentric Multidisciplinary Study

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What's known on the subject? and What does the study add?

Kidney stones can develop because of specific changes in the kidney tissue due to various diseases such as type 2 diabetes, hypertension, metabolic syndrome, and non-alcoholic fatty liver. Particularly, a triple mechanism is recognized between metabolic syndrome, non-alcoholic fatty liver disease and syndrome, and atherosclerosis the formation of kidney stones. To our results; triglyceride level and waist circumference were found to have a statistically significant effect on kidney stone formation. The formation of kidney stones caused by these risk factors in the patient can be prevented by eliminating these factors through preventable or treatable modifications.

Abstract

Objective: In this study, we examined the effects of dyslipidemia, obesity, non-alcoholic fatty liver disease and atherosclerosis on kidney stone formation.

Materials and Methods: Patients were divided into two groups; group 1; 300 patients having kidney stones or not group 2; 528 patients. Among these patients' triglyceride, cholesterol, high-density lipoprotein and low-density lipoprotein values; non-alcoholic fatty liver disease, atherosclerosis, waist circumference and subcutaneous adipose tissue thickness were recorded.

Results: It was determined that the presence of non-alcoholic fatty liver disease, atherosclerosis, high-density lipoprotein, low-density lipoprotein and cholesterol levels and subcutaneous adipose tissue thickness did not have any effect on developing kidney stones. However, triglyceride level and waist circumference had a statistically significant effect on kidney stone formation.

Conclusion: Considering that the presence of high triglyceride and low waist circumference levels can cause kidney stones in the patient; then the formation of kidney stones can be avoided by eliminating these factors through preventable or treatable modifications.

Keywords: Atherosclerosis, dyslipidemia, kidney stones, non-alcoholic fatty liver, obesity

Introduction

Kidney stone disease is a common health disorder worldwide. The lifetime incidence of developing a symptomatic kidney stone is 5-10% (1). The prevalence of kidney stones has been increasing worldwide in the recent years, and indeed in the Asian countries too, probably because of the westernization of Asian culture (2). The kidney stone formation is multifactorial, and it is revealed in epidemiological studies that male gender, age, race, climate, occupation, and obesity are the factors involved in this process (3,4).

Primarily, one or more factors are effective in kidney stone formation, including anatomical, metabolic, and nutritional causes. Additionally, kidney stones can also develop because of specific changes on the kidney tissue due to various diseases such as type 2 diabetes, hypertension, metabolic syndrome, and non-alcoholic fatty liver (5-8). Particularly, a triple mechanism

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is recognized between metabolic syndrome, non-alcoholic fatty liver disease syndrome, and atherosclerosis and the formation of kidney stones (9).

The pathophysiological mechanism that may clarify the underlying relationship between metabolic syndrome and kidney stone formation is not unclear. However, altered urine components decreased urine pH, decreased citrate excretion and increased uric acid and calcium excretion may be the cause of uric acid and calcium stones, in patients with metabolic syndrome (10-12).

It is obvious that there is a strong relationship between metabolic syndrome and kidney stone formation. However, there are very few studies in the literature that separately evaluate the effects of metabolic syndrome components, including dyslipidemia, obesity, hepatic manifestations of non-alcoholic fatty liver and cardiac manifestations of atherosclerosis (13). Such an inadequacy in the literature forced the requirement that these components should be evaluated specifically. In this study, we aimed to examine the effects of the above-mentioned factors on kidney stone formation and to protect patients from developing kidney stones by preventing and treating risk factors.

Materials and Methods

This study was conducted retrospectively after being reviewed and approved by the Institutional Review Board (approval number: 276). Informed consent was obtained from all patients when they were enrolled; in addition, the principles of the Declaration of Helsinki were followed. Our study was conducted jointly with 3 different urology clinics who collected the data and 1 radiology clinic who evaluated computed tomography (CT); it has been carried out in a multicentric and multidisciplinary manner. All patients were admitted to the urology outpatient clinic between January 2018 and May 2020 and had stone protocol (low-dose) non-contrast abdominopelvic CT with suspicion of kidney stones was reviewed. And those having triglyceride, cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) results were included in the study. Finally, they were divided into 2 groups concerning kidney stone formation: Group 1, with stone or group 2, without stone, regardless of the stone size. The study was conducted with 828 patients, 300 patients in group 1 and 528 patients in group 2.

The patients between the ages of 18-80, of both genders, and those who reported no alcohol usage in their anamnesis to exclude alcohol-induced fatty liver disease were included. Those with artefacts in their CT, with solitary kidney or kidney anomalies, nephrocalcinosis, kidney failure, known cancer diagnosis, non-renal urinary tract stones, cirrhosis or related ascites, acute or chronic hepatitis, and chronic liver disease were excluded from the study.

Stone protocol CT for urinary stone disease was applied (Siemens Healthcare, Germany). The patient was in the supine position when the imaging was performed. Images were taken between the diaphragmatic dome and inferior pubic ramus in sagittal and coronal sections with a slice thickness of 5 mm.

Non-alcoholic fatty liver definition was defined as mean CT liver attenuation ≤40 Hounsfield units by measuring at least 5 liver segments. The presence of atherosclerosis was accepted as arterial-wall calcifications on CT, abdominal aorta involving the main iliac arteries. Waist circumference was determined by measuring the abdominal circumference the cross-section passing through the umbilical level on CT. Subcutaneous adipose tissue thickness was determined by taking the average of 3 measurements performed suprapubically at the intersection of both midclavicular lines and the iliac crest at the level of the umbilicus.

Statistical Analysis

The SPSS 23.0 (SPSS, Chicago) package program was used in the statistical analysis of data. Measures of central tendency and distribution such as number, percentage, mean and standard deviation were used for descriptive statistics, while Pearson's chi-square test was used to determine the differences between categorical variables. The compliance of numerical variables to normal distribution was tested by the Shapiro-Wilk normality test, and the difference between normally concordant independent variables was determined by the Student's t-test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 973 patients were examined with a view to being included in our study group. After the exclusion criteria were implemented, 828 patients were included in the study. Of these, 379 (45.7%) were female and 449 (54.2%) were male, with a mean age of 45.59 (17.14) years. As for the age range, 117 of the patients (14.1%) were <30 years; 452 (54.5%) were between 30 and 60 years and 259 (31.2%) were more than 60 years of age. The patients were divided into 2 groups as those with kidney stones (group 1), consisting 300 patients (36.2%), and those without kidney stones (group 2), consisting of 528 patients (63.7%). The demographic data of the patients are presented in Table 1. According to these results, there were statistically significant differences between the two groups with respect to age and gender.

The effects of some components of metabolic syndrome on kidney stone formation are shown in Table 1 and Figures 1-3. According to these results, it was determined that the presence of non-alcoholic fatty liver and atherosclerosis, as well as HDL, LDL and cholesterol levels and subcutaneous adipose tissue

thickness had no effect on the development of kidney stones. However, triglyceride level and waist circumference were found to have a statistically significant effect on kidney stone formation. A statistically significant correlation was determined between the increase in triglyceride level (p=0.007) and the decrease in waist circumference (p<0.001) and kidney stone formation.

Considering the subgroup analysis of the age and gender parameters statistically significant among the factors affecting the kidney stone formation; the effect of gender distribution in group 1 patients was examined on the patients with or without non-alcoholic fatty liver disease and the correlation is shown in Table 2. Hence, it was concluded that non-alcoholic fatty liver disease had no effect on male and female patients who developed kidney stones.

Table 3 however, shows the relationship between gender distribution in group 1 patients and patients with or without atherosclerosis. According to these results, atherosclerosis was found to be statistically significantly less in male patients with stones (p=0.048).

Table 1. Demographic data and effects of some components of metabolic syndrome on kidney stone formation

	Group 1	Group 2	p-value
Gender (n, %)			
Male	195 (43.4)	254 (56.6)	**<0.001**
Female	105 (27.7)	274 (72.3)	
Age (n, %)			
<30	58 (49.6)	59 (50.4)	**0.001**
30-60	167 (36.9)	285 (63.1)	
>60	75 (29.0)	184 (71.0)	
Non-alcoholic fatty liver (n, %)			
Yes	218 (37.3)	366 (62.7)	0.310
No	82 (33.6)	162 (66.4)	
Atherosclerosis (n, %)			
Yes	180 (38.1)	293 (61.9)	0.189
No	119 (33.6)	235 (66.4)	
Triglyceride; mean (SD)	167.80 (113.71)	142.19 (97.30)	**0.007**
HDL; mean (SD)	48.64 (18.72)	49.19 (16.94)	0.739
LDL; mean (SD)	107.46 (38.35)	106.99 (35.45)	0.892
Cholesterol; mean (SD)	185.62 (43.39)	182.89 (43.55)	0.525
Waist circumference (cm)	66.93 (22.36)	75.13 (24.72)	**<0.001**
Subcutaneous adipose tissue thickness (cm)	2.86 (1.80)	2.84 (1.94)	0.842

HDL: High density lipoprotein, LDL: Low density lipoprotein, SD: Standard deviation

Considering the subgroup analysis of the age in group 1 patients, the relationship between age and non-alcoholic fatty liver is shown in Table 4. According to these results, a statistically significant level of non-alcoholic fatty liver was determined in <30 years old group 1 patients (p=0.006).

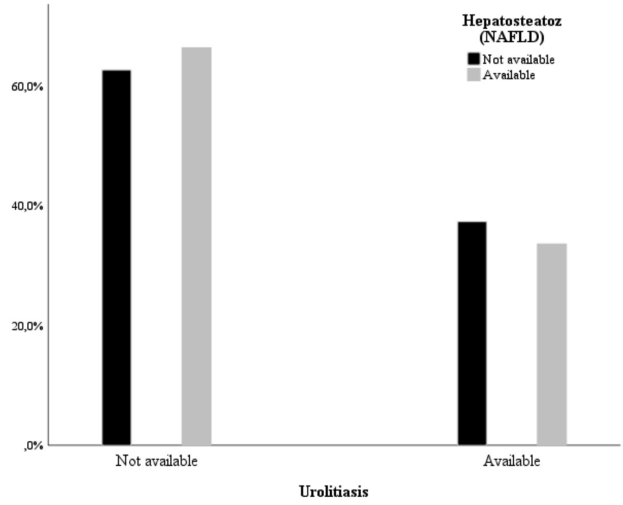

Figure 1. Relationship between non-alcoholic fatty liver disease and kidney stones

(NAFLD: Non-alcoholic fatty liver disease

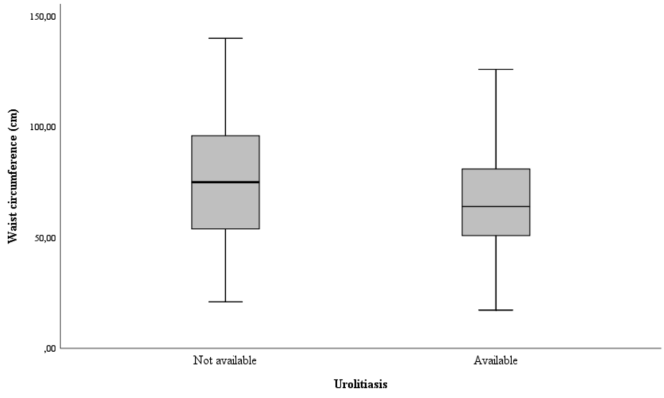

Figure 2. The effect of waist circumference on kidney stone formation

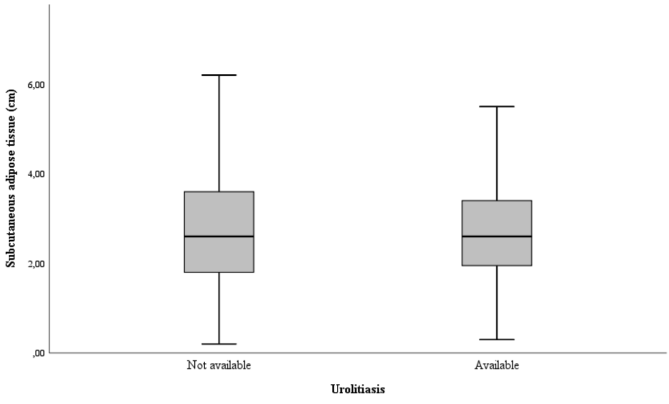

Figure 3. The effect of subcutaneous adipose tissue on kidney stone formation

Table 5 shows the relationship between the age distribution of patients in group 1 and the presence of atherosclerosis. According to these results, atherosclerosis was observed at a lower frequency in patients more than 60 years old in group 1 (14.6%) with respect to those ≤60 years old (p=0.038).

Discussion

No significant relationship was found between non-alcoholic fatty liver disease and kidney stone formation according to the results of our study, although there are studies in the literature indicating a significant correlation between them. For example, Nam (9) reported 19% higher prevalence of kidney stones in patients with non-alcoholic fatty liver disease. Again, Zeina et al. (14) obtained similar results in their study and concluded that the rate of kidney stones in patients with non-alcoholic fatty liver was significantly higher with an odds ratio of 3.4.

In a study conducted with 100 patients suspected of kidney stones due to renal colic, Paz et al. (15) determined a significant correlation between non-alcoholic fatty liver disease and kidney stones, especially in male patients. However, in our study, no significant relationship was found between kidney stones and non-alcoholic fatty liver disease in the gender subgroup analysis, although it was more common in men.

Table 2. Relationship between gender distribution in group 1 patients and non-alcoholic fatty liver disease

	NAFLD (+)	NAFLD (-)	p-value
Group 1; male (n, %)	59 (44.4)	136 (43.0)	0.796
Group 1; female (n, %)	23 (20.7)	82 (30.6)	0.051

NAFLD: Non-alcoholic fatty liver disease

Table 3. Relationship between gender distribution in group 1 patients and atherosclerosis

	Atherosclerosis (+)	Atherosclerosis (-)	p-value
Group 1; male (n, %)	81 (38.4)	113 (47.7)	**0.048**
Group 1; female (n, %)	38 (26.6)	67 (28.4)	0.702

Table 4. The relationship between age distribution of group 1 patients and non-alcoholic fatty liver disease

Age	NAFLD (-)	NAFLD (+)	p-value
<30 (n, %)	7 (100.0)	51 (46.4)	**0.006**
30-60 (n, %)	46 (34.3)	121 (38.1)	0.454
>60 (n, %)	29 (28.2)	46 (29.5)	0.817

NAFLD: Non-alcoholic fatty liver disease

Table 5. The relationship between age distribution of patients in group 1 and atherosclerosis

Age	Atherosclerosis (-)	Atherosclerosis (+)	p-value
<30 (n, %)	1 (100.0)	57 (49.1)	0.496
30-60 (n, %)	49 (36.3)	117 (37.0)	0.883
>60 (n, %)	69 (31.7)	6 (14.6)	**0.038**

Kim et al. (16) examined patients diagnosed with kidney stones ultrasonographically and the correlation between non-alcoholic fatty liver and kidney stones was determined only in male patients. Additionally, this correlation was observed only in patients under 50 years old. In comparison to this study, there was no correlation between kidney stones and non-alcoholic fatty liver disease in terms of gender in our study. However, the diagnosis of kidney stones was made by CT, which is the strength of our study as it is the gold standard method in this field, and a significant correlation was found between non-alcoholic fatty liver and kidney stones in patients under the age of 30.

The risk of kidney stones is associated with peripheral arterial vascular disease. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, an increase in carotid artery vascular wall thickness was determined in patients with kidney stones (17). Patel et al. (18) showed that calcification in the abdominal aorta on CT was associated with hypocitraturia, low urine pH and presence of kidney stones. According to the CT assessment of atherosclerosis in the abdominal aorta in our patients, no relationship was detected between kidney stone formation and the presence of atherosclerosis in the patient groups with and without stones. In the gender subgroup analysis, an inverse relationship was found between the presence of atherosclerosis and kidney stone formation in male patients with stones, and this inverse relationship increased significantly in patients >60 years old.

There are risk factors and mechanisms that seem independent from each other, such as insulin resistance, affecting the formation of kidney stones (17). For example, insulin contributes to ammonia production in the renal tubules (19). In case of insulin resistance developing with obesity, impaired insulin function causes altered ammonia synthesis and results in low urine pH; that is, it contributes to the favored urine acidity for uric acid crystallization and stone formation (20). Similarly, obesity is one of such risk factors. Waist circumference is a metric indicator of visceral obesity. Inflammatory cytokines released from adipocytes increase with the increase in subcutaneous adipose tissue (21). When the two patient groups in our study were compared, subcutaneous adipose tissue thickness displayed no effect on developing kidney stones; and we observed that waist circumference was significantly higher in the group without stones.

Inflammation, oxidative stress and lipotoxicity play a negative roles in the development of kidney stones (16). Inflammatory markers and pro-inflammatory cytokines may be elevated in patients with kidney stones. Lipotoxicity is another mechanism defined for altered kidney function, cellular damage and

hypoammoniagenesis in patients with kidney stones (7). Dyslipidemia is an independent risk factor for kidney stone formation, as it causes low urine pH (22). As for the lipid profile of our patient groups, cholesterol, HDL and LDL levels had no effect in both groups, whereas triglyceride level was significantly higher in the group with stones, in line with the abovementioned mechanism.

Study Limitations

Our study has some limitations. The most important is the bias risk of the CT performed in patients. Additionally, the retrospective design of our study, incomplete data regarding liver function tests of the included patients and types of renal stones of group 1 patients are the other limitations.

Conclusion

The high prevalence of metabolic syndrome or its components reveals the significance of our study, which has important results that may affect public health, based on the increased morbidity and mortality due to these risk factors. Kidney stones may be the result of a systemic disease and may have developed as a consequence of the relationship of many metabolic risk factors. The formation of kidney stones caused by such risk factors in the patient can be prevented by eliminating these factors through preventable or treatable modifications.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Local Ethics Committee Institutional Review Board (approval number: 276).

Informed Consent: Informed consent was obtained from all patients when they were enrolled.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.E., H.T., M.K., H.Y., Concept: B.E., H.T., Design: B.E., Data Collection or Processing: B.E., H.Y., M.K., Analysis or Interpretation: H.T., Literature Search: B.E., H.T., M.K., Writing: B.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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