

Relationship between urolithiasis and diastolic functions of the heart

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Aim: Relationships between urolithiasis and cardiovascular disorders were evaluated in several studies. In this study, we aimed to investigate whether urolithiasis causes a decline in cardiac diastolic functions.

Materials and methods: Seventy-seven consecutive patients and 40 age- and sex-matched controls were included in this study. Transthoracic echocardiography was performed for all patients.

Results: There were 77 patients (mean age: 45 ± 14 years, 64% male) in the stone-formers group and 40 patients (mean age: 43 ± 12 years, 63% male) in the control group. Peak E wave velocity (0.67 ± 0.21 to 0.85 ± 0.18, P = 0.001) and E/A ratio (0.97 ± 0.21 to 1.37 ± 0.27, P = 0.001) were significantly lower in stone formers than in control patients. In addition, peak A wave velocity (0.74 ± 0.15 to 0.69 ± 0.14) was significantly higher in stone formers than control patients (P = 0.01). Diastolic dysfunction was more frequent in stone formers than control patients (P = 0.015).

Conclusion: This study shows that there is a link between urolithiasis and cardiac diastolic dysfunction. Urolithiasis should therefore be recognized in evaluation of patients with diastolic dysfunction.

Key words: Urinary system, urolithiasis, diastolic dysfunction

1. Introduction

Prevalence of urinary system stone disease is high and varies from 2% to 20% in the general population (1). Urolithiasis causes physical discomfort and increased healthcare costs due to frequent recurrence. Various environmental and genetic factors play roles in the development of urinary stone disease (2). Relationships between urolithiasis and cardiovascular disorders were previously evaluated in several studies and a significant relation between urolithiasis and hypertension, cardiovascular mortality, and cardiovascular disease risk factors including smoking and hypercholesterolemia was shown (3,4). It was also found that prior occurrence of nephrolithiasis is associated with development of hypertension (5).

Diastolic dysfunction is defined as an increase in diastolic filling pressure to maintain normal cardiac output (6). Left ventricular diastolic dysfunction is considered as a precursor for systolic heart failure (7). It is well known that reduction in functional capacity is similar in patients with diastolic dysfunction and systolic dysfunction (8),

while 40%–50% of patients who present with symptoms of heart failure have a normal ejection fraction, which is defined as diastolic heart failure (9). It is currently well known that diastolic dysfunction plays an important role in the etiopathogenesis of cardiomyopathies, valve diseases, ischemic heart disease, and arterial hypertension (10). There are also many studies reporting the association between diastolic dysfunction and increased all-cause mortality (11).

Therefore, it is important to determine the etiological disorders that may be associated with diastolic dysfunction. In this study we aimed to investigate whether there is an association between urolithiasis and diastolic dysfunction.

2. Materials and methods

Seventy-seven patients (48 males and 29 females) diagnosed with urolithiasis by ultrasonography and intravenous urography (59 nephrolithiasis and 18 ureterolithiasis cases) in the Urology Department of the Erciyes University Medical School (Kayseri, Turkey)

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between January 2009 and April 2010 were included in this study. All patients with urolithiasis were then referred for extracorporeal shock wave lithotripsy (ESWL). Patients who had diabetes mellitus, hypertension, known coronary artery disease, or known heart failure history; were under diuretic therapy or had other cardiovascular disease history including valvular heart disease and pulmonary hypertension, metabolic syndrome, or neoplasm; were using drugs that could affect urate metabolism (allopurinol or a high-dose acetyl-salicylate); had chronic kidney disease (glomerular filtration rate less than 60 mL/min) or thyroid and parathyroid disease; or were under antihyperlipidemic treatment were excluded. Subjects with chronic diarrhea, urinary tract infection including pyelonephritis or pyonephrosis, or use of medications or treatment for renal stones (thiazide, alkali therapy) were also excluded. Forty age- and sex-matched (26 male and 14 female) individuals that presented to our clinic for routine check-up and were understood not to have urinary tract stones by medical history and urinary ultrasonography were randomly selected as control subjects. All exclusion criteria were applied to both patients and controls. The stones were analyzed following ESWL with infrared spectroscopy. Fasting (12 h) venous blood samples (6–8 mL) were collected from each subject. The study protocol was approved by the local ethics committee.

2.1. Echocardiographic examination

All patients were imaged in the left lateral decubitus position using the same echocardiographic system by 2 blinded cardiologists (VIVID 7, GE Vingmed Ultrasound, Horten, Norway). Evaluations of left ventricular systolic and diastolic diameter, left ventricular ejection fraction, valvular function, and diastolic function were performed in all patients and controls.

Two-dimensional pulsed-wave Doppler and color tissue Doppler imaging data were obtained in apical 4-chamber view during end-expiration. Mitral E and A velocities, E/A ratio, E deceleration time (EDEC), and E/E' measurements were performed in all patients.

An E/A ratio of <1 was defined as a criterion for diastolic dysfunction. Assessment of color M-mode flow propagation recordings were performed in the apical 4-chamber view. The M-mode cursor was positioned through the center of the left ventricular (LV) inflow in parallel to avoid boundary regions. The flow propagation velocity (Vp) was measured as the slope of the first aliasing velocity during early filling, measured from the mitral valve plane to 4 cm distally into the LV cavity. A Vp of more than 50 cm/s was considered as a normal value. Diagnosis of diastolic dysfunction and grading was performed according to American Society of Echocardiography (ASE) guidelines (12).

Blood pressure was measured with a random-zero sphygmomanometer by trained observers 2 times. The average of 2 measurements was noted and used in statistical analysis. Participants with systolic blood pressure (BP) of ≥ 140 mmHg and/or diastolic BP of ≥ 90 mmHg, or undergoing current antihypertensive drug treatment, were defined as hypertensive and excluded from the study.

2.2. Statistical analysis

All analyses were carried out using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were given as mean \pm standard deviation; categorical variables were defined as percentages. The variables were investigated using the Kolmogorov–Smirnov test to determine whether or not they were normally distributed. An independent samples t-test was used to compare continuous variables between the 2 groups. Nonparametric values were compared with the Mann–Whitney U test. The chi-square test was used to compare categorical data. A 2-tailed P value of <0.05 was considered as significant.

3. Results

Seventy-seven patients (mean age: 45 ± 14 years, 64% male) with urinary system stone disease and 40 age- and sex-matched control subjects (mean age: 43 ± 12 years, 63% male) were included in this cross-sectional study. In patients with urolithiasis, mean duration of disease was 1.5 ± 0.6 years. No significant differences were found between the 2 groups regarding age, sex, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, and serum lipids (Table 1). Hemoglobin, platelet count, white blood cell count, uric acid, and calcium levels were also similar in the 2 groups (Table 1). The types of the urinary stones found in the stone formers are shown in Table 2.

Echocardiographic findings are shown in Table 3. There were no significant differences between the 2 groups regarding LV ejection fraction, LV end-systolic and end-diastolic dimensions, LV fractional shortening, systolic pulmonary artery pressure, LV mass index, and left atrium dimension (Table 3).

Peak E wave velocity (0.67 ± 0.21 to 0.85 ± 0.18 , $P = 0.001$) and E/A ratio (0.97 ± 0.21 to 1.37 ± 0.27 , $P = 0.001$) were significantly lower in stone formers than control patients. In addition, peak A wave velocity (0.74 ± 0.15 to 0.69 ± 0.14 , $P = 0.01$) was significantly higher in stone formers than control patients. E wave deceleration time (144 ± 38 ms to 151 ± 32 ms, $P = 0.619$) and E/E' ratio (7.07 ± 3.1 to 6.65 ± 1.4 , $P = 0.131$) were similar among patients in both groups. There were also no significant differences between groups in terms of isovolumetric relaxation time and isovolumetric contraction time (Table 3). Diastolic dysfunction as determined according to ASE guidelines was more frequent in stone formers than controls (Table 3; Figure).

Table 1. General characteristics of study subjects.

	Stone formers (n = 77)	Controls (n = 40)	P-value
Age	45 ± 14	43 ± 12	0.531
Male	49 (64%)	25 (63%)	0.904
Mean duration of urolithiasis (years)	1.5 ± 0.6		
Systolic BP (mmHg)	135.5 ± 11.6	122.8 ± 9.3	0.056
Diastolic BP (mmHg)	84.3 ± 11.6	82.7 ± 10.4	0.231
Heart rate (beats/min)	74.6 ± 9.8	78.1 ± 8.9	0.129
Triglyceride (mg/dL)	142.1 ± 32.7	138.5 ± 29.8	0.395
LDL (mg/dL)	107.3 ± 22.6	104.2 ± 21.9	0.773
HDL (mg/dL)	35.3 ± 5.3	37.9 ± 5.8	0.413
Total cholesterol (mg/dL)	171.0 ± 25.9	169.8 ± 24.9	0.765
GFR (mL min ⁻¹ 1.73 m ⁻²)	78 ± 23	83 ± 24	0.353
Hemoglobin (g/dL)	14.3 ± 1.7	14.7 ± 1.6	0.323
Platelet count (/mm ³)	242 ± 63	251 ± 66	0.541
WBC (10 ³ /μL)	8.6 ± 4.3	8.1 ± 4.2	0.352
Uric acid level (mg/dL)	5.9 ± 1.7	5.6 ± 1.1	0.316
Calcium (mg/dL)	8.7 ± 1.1	9.1 ± 1.2	0.254
BMI (kg/m ²)	22.6 ± 5.3	24.3 ± 4.9	0.149

Data are expressed as mean ± standard deviation for normally distributed data and percentage for categorical variables. BP: Blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, GFR: glomerular filtration rate, WBC: white blood cell count, BMI: body mass index.

4. Discussion

The present study demonstrates a clear association between urolithiasis and diastolic dysfunction. In patients with urolithiasis, the E/A ratio, which is an indicator of diastolic function, is significantly impaired.

Several epidemiologic studies have recently demonstrated that more than 40%–50% of patients who were admitted to a hospital with symptoms of heart failure have diastolic dysfunction, which is defined as diastolic heart failure (9,12–16). It has also been shown that patients with diastolic heart failure show better long-term survival than patients with systolic heart failure. However, hospital readmission rates account for 25% of the total cost of heart failure management (17). In addition, it has been previously demonstrated that diastolic dysfunction

is associated with poor prognosis and increased all-cause mortality (11). Interestingly, despite the economic impact of this condition, diastolic heart failure is not taken into consideration in most of the international clinical guidelines on HF management. To avoid adverse outcomes associated with diastolic dysfunction, it is therefore important to determine the etiological disorders that can lead to diastolic dysfunction.

Several conditions, such as coronary artery disease, hypertension, congestive heart failure, valvular heart disease, endocrine diseases, and obesity, play roles in the development of diastolic dysfunction (18–20). In the present study, we prospectively enrolled patients without any medical issues that can lead to diastolic dysfunction, including coronary artery disease, hypertension, diabetes mellitus, valvular heart disease, obesity, and hypercholesterolemia, in order to evaluate the lone effect of urolithiasis on diastolic cardiac functions.

Previously, substantial amounts of data have shown the relation between hypertension and diastolic dysfunction. In addition, the relation between hypertension and urolithiasis has already been demonstrated. Madore et al. (21) found a significant relationship between hypertension and the development of urolithiasis. In the Olivetti Prospective Heart Study (22), the presence of urinary stone disease was found as an important predictor

Table 2. Type of the stones found in stone formers.

Type of stone	Percentage
Calcium-oxalate	60%
Uric acid stones	17%
Calcium-phosphate	10%
Struvite or infection	10%
Cystine or others	3%

Table 3. Comparison of echocardiographic parameters between stone formers and controls.

	Stone formers (n = 77)	Controls (n = 40)	P-value
LVEF (%)	64.8 ± 8	64.4 ± 9	0.731
LVFS (%)	38 ± 7	36 ± 7	0.435
LVSD (mm)	29 ± 6	30 ± 5	0.642
LVDD (mm)	45 ± 5	48 ± 4	0.434
sPAP (mmHg)	24.5 ± 6	26.1 ± 3	0.593
LVMI (g/m ²)	176 ± 16	166 ± 12	0.260
LA dimension (mm)	35 ± 9	36 ± 8	0.191
E wave (m/s)	0.67 ± 0.21	0.85 ± 0.18	0.001
A wave (m/s)	0.74 ± 0.15	0.69 ± 0.14	0.01
E/A ratio	0.97 ± 0.21	1.37 ± 0.27	0.001
EDEC (ms)	144 ± 38	151 ± 32	0.619
E/E' (mitral/lateral)	7.07 ± 3.1	6.65 ± 1.4	0.131
Isovolumetric relaxation time (ms)	80.6 ± 22.1	77.8 ± 22.6	0.309
Isovolumetric contraction time (ms)	55.5 ± 24.1	59.5 ± 1.5	0.121
Diastolic function			
Grade 1	27 (35%)	5 (13%)	0.015
Grade 2	7 (9%)	2 (5%)	
Grade 3	0 (0%)	0 (0%)	

Data are expressed as mean ± standard deviation for normally distributed data and percentage for categorical variables. LVEF: Left ventricular ejection fraction, LVFS: left ventricle fractional shortening, LVSD: left ventricular systolic diameter, LVDD: left ventricular diastolic diameter, sPAP: systolic pulmonary artery pressure, LVMI: left ventricular mass index, LA: left atrium, EDEC: E deceleration time.

for development of overt hypertension after 8 years of follow-up in middle-aged men. While some researchers suggested that the presence of urolithiasis is a precursor for hypertension development (23), some others suggested that hypertension is a precursor for urinary stone formation (20,24).

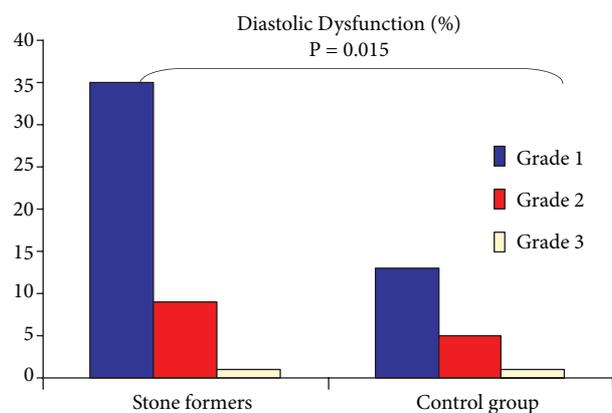


Figure. Rates of diastolic dysfunction compared between stone formers and controls.

The mechanism by which urinary stones could increase the risk for diastolic dysfunction is not clear. However, some physiopathological mechanisms may be proposed to explain this association. Calcification and deposition of calcium in various parts of the cardiovascular system in patients with urolithiasis are well known. In a study by Yasui et al., the aortic calcification score detected by abdominal computed tomography was found to be significantly higher in patients with urolithiasis when compared with healthy controls (25). In another study conducted by Celik et al., a clear association was demonstrated between urolithiasis and mitral annular calcification, despite similar serum calcium levels of patients with renal stone and healthy controls (26). There are also several studies reporting an association between coronary atherosclerosis and kidney stones. In a study by Rule et al. (27), an increased risk for myocardial infarction was found in kidney stone formers, and this risk was independent of chronic kidney disease and other risk factors. Calcium oxalate stone formation was also shown to be associated with several coronary heart disease risk factors, including smoking habit, hypertension, hypercholesterolemia, and obesity (28,29).

Schlieper et al. mentioned a probably common pathway playing a role in the calcification of various tissues, such as in the urinary system and cardiovascular system (30). Calcification in the cardiovascular system is the most threatening complication of this unwanted calcification. The similarities in development of urolithiasis and cardiac diastolic dysfunction give rise to the thought that both of these diseases might be components of a systemic disorder leading to unwanted calcification. Schlieper et al. reported that, in the cardiovascular system, unwanted calcification mostly develops in coronary arteries and the medial layer of the aorta, leading to aortic stiffness. Aortic stiffness and loss of elasticity of the aorta increases the afterload and causes cardiac diastolic dysfunction. The myocardium itself may also be affected by calcification with the same mechanism. Calcification of both coronary arteries and especially the aorta may explain the presence of diastolic dysfunction in our patients with urolithiasis.

To the best of our knowledge, this is the first study to show the association between urinary system stone

disease and diastolic dysfunction. However, it is not clearly known yet which mechanism is responsible for diastolic dysfunction in patients with urinary system stone disease. Larger studies are needed to clearly establish this relationship and to clarify the underlying mechanisms leading to diastolic dysfunction in patients with urolithiasis.

Our study has some limitations to be mentioned. First, the sample size of our study was relatively small. Prospective studies with larger sample sizes are needed to justify our results. Second, usage of more detailed biochemical tests, such as urine analyses, would probably provide additional information on the relationship between urinary system stone disease and diastolic dysfunction.

In conclusion, the present pilot study shows that there is a relation between urinary system stone disease and cardiac diastolic dysfunction. Therefore, patients with urolithiasis should have a detailed echocardiographic evaluation.

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