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Assessment of Cardiac Functions and Subclinical Cardiovascular Risk in Children with Urolithiasis: A Pilot Study

Ahmet Midhat Elmacı[1], Hayrullah Alp[2], Muhammet İrfan Dönmez[3]

[1]Karamanoğlu Mehmet Bey University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Nephrology, Karaman, Turkiye
[2]Karamanoğlu Mehmet Bey University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Cardiology, Karaman, Turkiye
[3]İstanbul University, İstanbul Faculty of Medicine, Department of Urology, Division of Pediatric Urology, İstanbul, Turkiye

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

The incidence of urolithiasis is increasing globally. Chronic inflammation is associated with subclinical atherosclerosis. Subclinical atherosclerosis, in addition to early systolic and diastolic dysfunction, is observed in children with urolithiasis.

Abstract

Objective: Information on cardiovascular problems related to childhood urinary stone disease is limited. The aim of this study was to assess the ventricular functions and subclinical cardiovascular risk in children with urolithiasis using echocardiographic measurements.

Materials and Methods: Children diagnosed with urolithiasis were prospectively enrolled in the study as well as children with no urinary stone disease were confirmed via urinary ultrasonography. Body mass index and blood pressures were noted, as well as basic serum parameters. Carotid intima media thickness (cIMT), epicardial fat tissue (EFT) thickness and periaortic fat tissue (PFT) thickness were measured via transthoracic echocardiography in addition to pulsed and tissue Doppler imaging. Myocardial performance indexes were also calculated and correlation analyses were conducted.

Results: A total of 17 patients (10 boys) with a mean age of 8.57±2.62 years were included in this study. There were 17 children (12 boys) in the control group and their mean age was 9.53±1.72 years. There was no statistically significant difference between the two groups in terms of demographic and laboratory variables. Tissue Doppler echocardiography revealed that Tei indexes of the left ventricle, right ventricle and septum were significantly higher in the study group than in the controls ($p<0.001$ for all). The cIMT (0.041±0.012 vs. 0.025±0.002), EFT (0.432±0.083 vs. 0.325±0.032) and PFT thicknesses (0.138±0.029 vs. 0.113±0.008) of the study group was statistically higher than the control group ($p<0.001$, $p<0.001$ and $p=0.002$, respectively) indicating a higher CVD risk.

Conclusion: Children with urolithiasis had not only biventricular early systolic and diastolic dysfunction but also subclinical atherosclerosis at early ages. Cardiovascular complications should be considered in the follow-up and treatment of children with urolithiasis.

Keywords: Urolithiasis, subclinical atherosclerosis, cardiovascular risk, children

Introduction

Urolithiasis is a global disease with increasing prevalence recently and it causes significant morbidity for all ages. In the USA, 11% of men and 7% of women are diagnosed with urinary stone disease throughout their lives (1). Further, recurrences may be observed in 30% to 50% of the cases in 5-10 years after the first stone incidence (2). On the other hand, chronic inflammation is an independent factor for subclinical atherosclerosis and thus, cardiovascular complications. It was shown that inflammatory cytokines play a role in the progression of atherosclerosis (3). Studies in the adult population indicated that urolithiasis is related to chronic systemic inflammation such as hypertension, diabetes and metabolic syndrome. Also, it has been demonstrated

Correspondence: Muhammet İrfan Dönmez MD, İstanbul University, İstanbul Faculty of Medicine, Department of Urology, Division of Pediatric Urology, İstanbul, Turkiye
Phone: +90 212 414 24 56 **E-mail:** m_irfan83@yahoo.com **ORCID-ID:** orcid.org/0000-0002-2828-7942
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that myocardial infarction, stroke and coronary artery disease are more commonly found in patients with urinary stone disease (4). A recent study that looked into adolescents with urolithiasis reported increased levels of urinary cytokines that mention the presence of chronic inflammation (5).

Furthermore, studies showed oxidative stress and inflammation induces Randall's plaque, which is the initial step in stone formation (6). In CARDIA study, researchers revealed a positive correlation between urolithiasis and subclinical atherosclerosis in young adults (7). To date, a single study investigated atherosclerosis and cardiovascular complications in children which showed Carotid intima media thickness (cIMT) that is a sign of subclinical atherosclerosis was increased in children with nephrolithiasis this study (8).

In current practice, cIMT is used as a marker to identify subclinical atherosclerosis and epicardial fat tissue (EFT) thickness and periaortic fat tissue (PFT) thickness. Several researchers demonstrated the use of these markers of subclinical atherosclerosis in different chronic diseases in the pediatric population (9,10). The aim of this initial prospective case-control study was to assess the risk of subclinical cardiovascular risk in children with urolithiasis using cIMT, EFT and PFT thickness in addition to tissue Doppler imaging (TDI) echocardiographic evaluation of cardiac functions. Our hypothesis was children with urolithiasis would show signs of systemic inflammation in terms of echocardiographic assessments.

Materials and Methods

Patients

After obtaining by the Institutional Reviewer Board of Konya Chamber of Commerce University (number: 419011325-050.99), patients were prospectively included for this study between December 2019 and May 2020. Patients >5 years of age and had kidney stones (>3 mm) that were confirmed by two consecutive ultrasonographic images or computed tomography and those had normal serum chemistry were included in the study. Those with congenital heart disease, chronic kidney disease, inflammatory bowel disease, monogenic stone phenotypes, urogenital malformations (vesicoureteral reflux, posterior urethral valves, neuropathic bladder etc.), obesity, hypertension, chronic diseases (i.e., diabetes mellitus) and patients who were passive smokers were excluded. The control group consisted of health children who have normal BMI and blood pressure (adjusted for age) with no known history of urolithiasis (confirmed by urinary ultrasonography). All parents gave informed consent for inclusion.

Blood pressures were measured from the left arm using age-appropriate manual sphygmomanometer cuffs after 5 min of resting and a mean of 3 measurements were noted. All blood samples including urea, creatinine, glucose, uric acid, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) were obtained a.m. after 8 h of fasting. Glomerular Filtration Rate (GFR) was calculated by Schwartz formula (11). Echocardiographic measurements were performed as previously described (12).

Statistical Analysis

The compatibility of numerical variables to normal distribution was examined using the Shapiro-Wilk test. Descriptive findings were presented as number, percentage mean and standard deviation. Comparisons between groups were made using chi-square test for categorical variables, and t-test for independent groups if assumptions were met for numerical variables, otherwise by Mann-Whitney U test. Statistical significance level was set as $p<0.05$.

Results

A total of 17 patients, 10 boys and 7 girls (41% and 59%), were enrolled in the study. Mean age of the study group was 8.57±2.62 years (range years). Eleven (64.7%) of the patients in the study group had a positive family history for urolithiasis, 10 (58.8%) had multiple stones, 6 (35.3%) had bilateral stones. Mean stone size was 8.6±4.3 mm and mean follow-up period was 16.2±9.3 months. In terms of metabolic abnormality, 7 (41.2%) had hypocitraturia, 4 (23.5%) had hypercalciuria, 2 (11.8%) had hyperoxaluria, while no abnormalities were detected in 4 (23.5%). At the time of enrollment, 8 (47.1%) children were on medical treatment (in the form of oral potassium citrate), 4 (23.5%) and 5 (29.4%) have undergone Extracorporeal Shock Wave Lithotripsy and surgical treatment (3 ureterorenoscopic intervention, 2 percutaneous nephrolithotomy), respectively. There were 12 boys and 5 girls (71% and 29%) in the control group with a mean age of 9.53±1.72 years. There was no significant difference between the two groups in terms of age, gender, blood pressure, BMI, serum lipids, hemoglobin and GFR (Table 1).

There was no statistical difference between the M-mode echocardiography, LVM and LVMI results of the study and control groups (Table 2). Pulsed Doppler echocardiographic evaluation revealed that; LV ejection time (261.71±21.09 vs. 279.59±28.51, p=0.046) was significantly shorter in the study group. Additionally, while LV MPI (0.283±0.27 vs. 0.166±0.07, p=0.013) was significantly higher in the study group, the tricuspid valve E/A ratio (1.13±0.24 vs. 1.29±0.19, p=0.026) was statistically lower for the same group (Table 3).

Tissue Doppler echocardiography measurements revealed that; mitral valve lateral annulus e' (11.34±2.08 vs. 16.23±3.16,

Table 1. Demographic and laboratory data of study population			
	Patients (n=17)	Controls (n=17)	p
Age (years)	8.57±2.62	9.53±1.72	0.214
Gender (male/female)	10/7	12/5	0.473
BMI (kg/m²)	16.09±2.83	16.50±2.01	0.592
BMI Z-score	0.09±1.43	-0.28±0.81	0.391
SBP (mmHg)	98.82±8.58	98.24±8.09	0.865
DBP (mmHg)	63.37±6.17	64.71±6.29	0.423
Glucose (mg/dL)	93.94±12.94	95.41±7.99	0.693
eGFR (mL/min/1.73 m²)	91.03±10.82	92.94±9.06	0.586
Uric acid (mg/dL)	3.98±0.78	3.89±0.62	0.702
Total cholesterol (mg/dL)	160.55±44.82	152.71±24.98	0.539
Triglyceride (mg/dL)	102.17±74.95	81.35±24.47	0.287
LDL-C (mg/dL)	93.03±37.56	83.75±26.96	0.596
HDL-C (mg/dL)	52.61±13.61	47.53±9.72	0.249
Hemoglobin (g/dL)	13.04±0.74	13.19±0.78	0.562
CRP (mg/dL)	2.46±1.31	2.31±1.53	0.436

Data are expressed mean ± standard deviation. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, eGFR: Estimated glomerular filtration rate, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, CRP: C-reactive protein

Table 2. M-mode echocardiographic measurements in patients with urolithiasis and control groups			
	Patients (n=17)	Controls (n=17)	p
	Mean ± SD	Mean ± SD	
IVSd (cm)	0.69±0.18	0.67±0.14	0.838
IVSs (cm)	1.09±0.22	1.10±0.20	0.876
LVPWd (cm)	0.71±0.10	0.64±0.18	0.180
LVPWs (cm)	1.12±0.21	1.17±0.21	0.342
LVEdD (cm)	3.79±0.39	3.82±0.36	0.121
LVEsD (cm)	2.21±0.26	2.28±0.27	0.350
EF (%)	72.98±3.44	72.86±10.54	0.23
FS (%)	41.26±3.19	39.45±3.59	0.130
LVM (gr)	66.18±29.26	70.57±24.44	0.322
LVMI (g/m$^{2.7}$)	32.59±12.14	29.85±4.95	0.433

IVSd: Interventricular septum diastolic thickness, IVSs: Interventricular septum systolic thickness, LVPWd: Left ventricular posterior wall diastolic thickness, LVPWs: Left ventricular posterior wall systolic thickness, LVEdD: Left ventricular end-diastolic dimension, LVEsD: Left ventricular end-systolic dimension, EF: Ejection fraction, FS: Fractional shortening, LVM: Left ventricular mass, LVMI: Left ventricular mass index

p<0.001), a' (7.07±1.11 vs. 8.49±2.14, p=0.021), tricuspid valve lateral annulus e' (11.67±1.66 vs. 13.56±1.94, p=0.005), interventricular septum e' (9.26±1.69 vs. 13.46±2.34, p<0.001) and a' velocities (5.39±0.89 vs. 6.43±1.17, p=0.007) were significantly decreased in the study group than in controls (Table 4). However, time intervals including IVCT (isovolumic contraction time) measured from tricuspid valve lateral annulus (53.12±8.43 vs. 47.06±6.49, p=0.025) and interventricular septum (53.53±6.86 vs. 47.41±7.63, p=0.020), IVRT (isovolumic relaxation time) measured from tricuspid lateral annulus (58.41±8.91 vs. 51.88±8.40, p=0.035) and interventricular septum (55.47±6.77 vs. 47.41±8.64, p=0.005) were statistically increased in children with urolithiasis. Additionally, mitral valve lateral annulus contraction time (CT) (184.94±43.09 vs. 259.53±16.46, p<0.001), tricuspid valve lateral annulus CT (199.53±37.22 vs. 254.82±11.63, p<0.001) and interventricular septum CT (187.29±54.56 vs. 259.88±16.77, p<0.001) were significantly lower in the urolithiasis group. Also, e'/a' ratios measured from mitral valve lateral annulus and interventricular septum were statistically lower in patients with urolithiasis (p=0.018 and 0.005, respectively). E/e' ratios measured from

Table 3. Pulsed Doppler echocardiographic measurements in patients with urolithiasis and control groups			
	Patients (n=17)	Controls (n=17)	p
	Mean ± SD	Mean ± SD	
Mitral valve blood flow			
Peak E (cm/s)	89.56±16.12	84.84±12.86	0.352
Peak A (cm/s)	60.51±15.95	59.52±10.94	0.834
E/A ratio	1.56±0.49	1.45±0.23	0.838
Tricuspid valve blood flow			
Peak E (cm/s)	61.21±10.41	62.29±7.45	0.322
Peak A (cm/s)	55.62±12.22	48.56±6.82	0.140
E/A ratio	1.13±0.24	1.29±0.19	**0.026**
LV ejection time (ms)	261.71±21.09	279.59±28.51	**0.046**
RV ejection time (ms)	263.76±24.89	271.29±19.66	0.341
LV MPI	0.283±0.27	0.166±0.07	0.013
RV MPI	0.231±0.24	0.166±0.08	0.658

Early (E) and late (A) mitral/tricuspid diastolic velocities, LV: Left ventricle, RV: Right ventricle, MPI: Myocardial performance index, SD: Standard deviation

LV was increased in the study group (p<0.001). Furthermore, Tei indexes of LV, RV and septum were significantly higher in urolithiasis patients than in controls (Table 4).

The cIMT (0.041±0.012 vs. 0.025±0.002), EFT (0.432±0.083 vs. 0.325±0.032) and PFT thickness (0.138±0.029 vs. 0.113±0.008) of the study group was statistically higher than the control group (p<0.001, p<0.001 and p=0.002, respectively) (Table 5). Post hoc power analysis for each variable was determined by taking at least 80% and Type-I error as 5%.

Discussion

Besides urinary tract obstruction and related renal damage, urolithiasis may also release inflammatory cytokines due to crystal storage and this has been associated with cardiovascular complications (13,14). Clinical and experimental studies have shown that there is a strong relationship between crystal adhesion and crystal formation in renal tubular cells and inflammation and oxidative stress (6,15). Taguchi et al. (16) demonstrated genes related to oxidative stress and stated that proinflammatory conditions were highly expressed in calcium oxalate stone formers than normal renal papillary tissue (16). Same group further demonstrated that M1 macrophages (inflammatory) stimulated renal calcium oxalate crystal deposition and M2 macrophages (anti-inflammatory) limited such crystal formation in a murine model of hyperoxaluria (14).

Clinically, cIMT is used as a reliable marker in the evaluation of atherosclerotic change in the early period. In some studies that evaluated the progression of atherosclerosis, a strong relationship has been reported between cIMT and IL-6 (17). cIMT was reported to show subclinical atherosclerosis in different chronic diseases of childhood (9). The only study in the literature in which cIMT was evaluated in children with urolithiasis, Kusumi et al. (5) found that cIMT was significantly higher in children aged 12-17 years and reported that urine osteopontin and fibronectin-1could predict elevated cIMT. Similarly, in our study, cIMT was significantly higher in children with urolithiasis than in the control group, and this shows subclinical atherosclerosis in patients with pediatric urolithiasis. However, mean age of our study group was lower than those included in their study. Thus, it can be suggested that subclinical atherosclerosis begins at an even earlier age in children with urolithiasis.

Body fat distribution is an important cardiovascular risk factor, and fat depositions are associated with all-cause deaths. One component of the abnormal body fat depot, called ectopic fat, is the accumulation of adipose tissue around organs and vessels. Ectopic adipose tissue, unlike subcutaneous adipose tissue, is not an ordinary place for lipid storage (18). Epicardial and periaortic adipose tissue, like other adipose tissues, has endocrine functions that can produce inflammatory cytokines and secrete hormones. Moreover, they have been recently identified as strong risk factors for cardiovascular disease due to their role in the inflammatory process in atherosclerosis (18,19). It was reported that EFT is a reliable parameter for cardiovascular risk in adult chronic kidney disease and EFT thickness can predict coronary artery disease (20). In obese children, an increase in EFT thickness was associated with coronary artery disease, magnified cIMT and arterial stiffness (21). Studies also showed that in non-obese children with neurological disabilities, EFT thickness was significantly higher and correlated with clinical and metabolic risk factors (22). Akyurek et al. (10) evaluated the relationship between PFT thickness and cardiovascular risk in 135 children with type-1 DM and they showed a positive

correlation between PFT thickness and cIMT and metabolic risk factors (10). In our study, EFT and PFT thicknesses were significantly higher in children with urolithiasis.

It is known that E/e' ratio shows the strongest correlation with LV/RV diastolic filling pressure and LV/RV compliance (23), whereas E/A and e'/a' ratio correlates with relaxation type dysfunction (24). Limited data from the children with chronic kidney diseases revealed that left ventricular E/A and e'/a' ratio decreases and E/e' ratio increases along with the worsening of renal functions from mild-moderate to severe renal failure (25).

Table 4. Tissue Doppler echocardiographic measurements in patients with urolithiasis and control groups

	Patients (n=17)	Controls (n=17)	p
	Mean ± SD	Mean ± SD	
Mitral valve lateral annulus			
e' (cm/s)	11.34±2.08	16.23±3.16	**<0.001**
a' (cm/s)	7.07±1.11	8.49±2.14	**0.021**
s' (cm/s)	11.04±3.48	9.55±3.07	0.205
IVCT (ms)	55.64±8.87	50.35±11.94	0.152
IVRT (ms)	57.00±12.91	50.18±7.80	0.071
CT (ms)	184.94±43.09	259.53±16.46	**<0.001**
e'/a' ratio	1.62±0.29	1.99±0.54	**0.018**
E/e' ratio	8.22±2.47	5.38±1.14	**<0.001**
Tricuspid valve lateral annulus			
e' (cm/s)	11.67±1.66	13.56±1.94	**0.005**
a' (cm/s)	9.18±2.19	9.43±1.37	0.690
s' (cm/s)	11.56±2.79	13.09±1.95	0.074
IVCT (ms)	53.12±8.43	47.06±6.49	**0.025**
IVRT (ms)	58.41±8.91	51.88±8.40	**0.035**
CT (ms)	199.53±37.22	254.82±11.63	**<0.001**
e'/a' ratio	1.32±0.26	1.46±0.26	0.136
E/e' ratio	5.14±1.59	4.68±0.91	0.314
Interventricular septum			
e' (cm/s)	9.26±1.69	13.46±2.34	**<0.001**
a' (cm/s)	5.39±0.89	6.43±1.17	**0.007**
s' (cm/s)	8.19±2.44	8.29±1.22	0.866
IVCT (ms)	53.53±6.86	47.41±7.63	**0.020**
IVRT (ms)	55.47±6.77	47.41±8.64	**0.005**
CT (ms)	187.29±54.56	259.88±16.77	**<0.001**
e'/a' ratio	1.74±0.36	2.13±0.39	**0.005**
LV Tei index	0.642±0.195	0.362±0.102	**<0.001**
RV Tei index	0.581±0.144	0.393±0.047	**<0.001**
Septum Tei index	0.639±0.229	0.366±0.049	**<0.001**

e': Peak early diastolic myocardial velocities, a': Peak atrial systolic myocardial velocities.
s': Peak systolic myocardial velocities, IVCT: Isovolumetric contraction time, IVRT: Isovolumetric relaxation time, CT: Contraction time, LV: Left ventricle, RV: Right ventricle

Table 5. cIMT, EFT and PFT thickness measurements in patients with urolithiasis and control groups

	Patients (n=17)	Controls (n=17)	p
	Mean ± SD	Mean ± SD	
cIMT (cm)	0.041±0.012	0.025±0.002	**<0.001**
EFT thickness (cm)	0.432±0.083	0.325± 0.032	**<0.001**
PFT thickness (cm)	0.138±0.029	0.113± 0.008	**0.002**

cIMT: Carotid intima-media thickness, EFT: Epicardial fat tissue, PFT: Periaortic fat tissue

However, Celik et al. (26) reported decreased E/A and increased e'/a' ratio in non-obese-treated hypertensive patients. These studies revealed the dysfunction of LV relaxation and diastolic filling pressures, however, right ventricular functions were not studied and possibly RV dysfunction was underestimated. In this context, our study revealed that the E/A ratio measured from RV and e'/a' ratio measured from LV were significantly lower in children with urolithiasis compared with healthy controls (p=0.026 and p=0.018, respectively). Additionally, E/e' ratio measured from LV was detected to be increased in the patient group. This finding suggests that LV function and diastolic filling pressures are worsened in children with urolithiasis.

Subsequently, MPI or Tei index is a good predictor of ventricular systolic functions in children and adults (27). MPI measured by PWD, M-mode and TDI methods are valuable parameters indicating systolic and parameters show worsening of these functions. The results from Celik et al. (26) showed that left ventricular MPI was higher in non-obese-treated hypertensive children, but no significance was achieved. However, in our study MPI values of LV was significantly higher in patients (p=0.013) while no statistical significance was shown in right ventricular MPI. Besides, both Tei index values of LV, RV and septum were significantly increased in the study group than in the controls (in all p<0.001). By this way, we demonstrated a significant reduction of systolic and diastolic functions of LV and RV in children with urolithiasis compared to healthy children.

Study Limitations

The main limitation of our study was the limited number of patients. Also, inflammatory cytokines have not been studied in patients, which is unfortunately, beyond the scope of our facility. However, extensive echocardiographic investigation was performed for both the study and the control group performed in this prospective study.

Conclusion

LV and RV early systolic and diastolic dysfunction, with subclinical atherosclerosis, were detected in children with urolithiasis in early ages. Cardiovascular complications should be considered in the follow-up and treatment of these patients, and the pediatric urolithiasis patients deserve further studies in terms of cardiovascular risks. Longitudinal studies with long-term follow-up will enlighten the adulthood consequences of these findings.

Ethics

Ethics Committee Approval: The approval of the research protocol by the Institutional Reviewer Board of Konya Chamber of Commerce University (number: 419011325-050.99).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.M.E., H.A., M.İ.D., Concept: A.M.E., H.A., M.İ.D., Design: A.M.E., H.A., M.İ.D., Data Collection or Processing: A.M.E., H.A., M.İ.D., Analysis or Interpretation: A.M.E., H.A., M.İ.D., Literature Search: A.M.E., H.A., M.İ.D., Writing: A.M.E., H.A., M.İ.D.

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