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Hyperuricemia is an Independent Predictive Factor for Left Ventricular Diastolic Dysfunction in Patients with Chronic Kidney Disease

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. It has been reported that elevated serum uric acid (UA) levels is an independent factor of poor prognosis in patients with chronic heart failure and chronic kidney disease (CKD).
Objectives. In our study, we assessed the potential impact of hyperuricemia on left ventricular (LV) diastolic dysfunction (DD) in patient with CKD.
Material and Methods. The study group consisted of 50 patients with CKD, stages 2–5. Standard echocardiography and tissue Doppler imaging (TDI) were performed. The levels of UA and N-terminal prohormone brain natriuretic peptide (NT-proBNP) were determined. Patients were divided into two groups according to the results of peak mitral annular early diastolic velocity (EmLV): group with LV diastolic dysfunction (EmLV < 8 cm/s) DD (+) and group with normal LV diastolic function DD (–), when EmLV ≥ 8 cm/s.
Results. Patients DD (+) group, as compared to DD (–) patients were characterized by significantly higher serum UA levels [6.7 (4.4–14.3) mg/dL vs 5.8 (1.9–8.9) mg/dL, p = 0.004] respectively. The area under the receiver operating characteristic (ROC) curve was of serum UA levels for the detection of LV diastolic dysfunction was 0.734, 95% confidence interval (CI) 0.590–0.849, p = 0.001, whereas ROC derived UA value of > 6.0 mg/dL was characterized by a sensitivity of 76.9% and specificity of 62.5% for diagnosing LV diastolic dysfunction. The independent variable predicting LV diastolic dysfunction as measured by a multivariate logistic regression analysis was UA level > 6.0 mg/dL with odds ratio (OR) = 14.3 (95% CI 2.0–103.2), p = 0.006.
Conclusions. Hyperuricemia is an independent predictive factor for LV diastolic dysfunction in patients with CKD (**Adv Clin Exp Med 2015, 24, 1, 47–54**).

Key words: chronic kidney disease, hyperuricemia, left ventricular diastolic dysfunction, echocardiography.

Uric acid (UA) is the end product of purine metabolism [1]. Elevated serum UA levels may be a result of increased production, reduced renal excretion, or of both situations. Many previous studies have confirmed the importance of hyperuricemia, an independent factor of poor prognosis in patients with hypertension, coronary artery disease, chronic heart failure and chronic kidney disease (CKD) [2–5]. Nevertheless, it has not completely explained the mechanism of the negative effects of hyperuricemia on the function of the heart muscle. It is known that hyperuricemia may cause cardiovascular complications by several mechanisms such as inflammation, activation of the renin-angiotensin-aldosteron (RAA) system, damage to endothelial cells, inhibition of secretion of nitric oxide (NO) [6, 7]. Therefore, we speculate that the mechanisms of action of UA, particularly the endothelium and the RAA system can impair the left ventricular diastolic function of the

heart. To our knowledge, there are only few studies on the direct effects of elevated levels of UA in diastolic dysfunction [8, 9]. In our study, we assessed a potential impact of hyperuricemia on left ventricular diastolic dysfunction in patients with CKD.

Material and Methods

The study group consisted of 50 patients with CKD, stages 2–5, with sinus rhythm and with preserved LV systolic function – left ventricular ejection fraction (LVEF) > 50%. Exclusion criteria comprised: non-sinus rhythm, LV global or regional systolic dysfunction, previous myocardial infarction, significant valvular heart disease, pericardial fluid > 10 mm at diastole. Diagnostic criteria for CKD were consistent with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) standards [10].

Echocardiography Examination

Standard echocardiography was performed in all patients using a GE 6S device with 2.5–3.5 MHz transducer. Using the M-MODE in the parasternal long-axis view the following parameters were assessed: left ventricular end-diastolic dimension (LVEDD), right ventricular end-diastolic dimension (RVEDD), left atrial diastolic dimension (LAD), interventricular septal diastolic diameter (IVSd) and left ventricular posterior wall dimension at diastole (LVPWd). In a 4-chamber view left ventricular ejection fraction (LVEF) was calculated with the modified Simpson's rule [11]. Left ventricular mass (LVM) was calculated with the formula recommended by the American Society of Echocardiography (ASE) modified by Devereux [12]. The obtained results of LVM were indexed by the body surface area of the patient and presented as left ventricular mass index (LVMI).

In order to assess transmitral flow, pulsed wave Doppler echocardiography was performed in a four chamber view. The Doppler gate was placed at the tips of the mitral valve leaflets and a 2-phase flow profile was obtained, including: early (E) and late (A) transmitral velocities, and deceleration time (DT) of the E wave; E/A ratio was also calculated [11].

Tissue Doppler Echocardiography Examination

Using pulsed wave tissue Doppler echocardiography systolic and diastolic velocities were measured by placing the Doppler gate on the lateral mitral annulus at the posterior leaflet of the mitral valve. The following parameters were measured: peak mitral annular systolic velocity (SmLV), peak early diastolic velocity (EmLV) and peak late diastolic velocity (AmLV) of the lateral part of the examined annulus [13]. The ratio of early transmitral peak velocity (E) to the mitral annular early diastolic velocity (EmLV) was used as an approximation of mean left atrial pressure (E/Em). All parameters were calculated as the mean of measurements taken in 3 consecutive cardiac cycles. LV diastolic dysfunction (DD) was defined as EmLV < 8 cm/s [14].

Patients were divided into 2 groups depending on the results of EmLV: DD (+) group with LV diastolic dysfunction (EmLV < 8 cm/s) and DD (–) group with normal LV diastolic function, when EmLV ≥ 8 cm/s.

Biochemical Tests

On the day of the echocardiographic examination, the following laboratory parameters were recorded for all patients: serum creatinine concentration, estimated glomerular filtration rate (eGFR) evaluated by the modified MDRD formula, as well as the serum levels of urea, phosphorus (P), calcium (Ca), parathormone (PTH), platelets (PLT), hemoglobin (Hb). Additionally, N-terminal prohormone brain natriuretic peptide (NT-proBNP) level was measured by immunoassay with the Stratus® CS Acute Care™ Siemens and serum uric acid (UA) was assessed using the uricase method [15].

Statistical Analysis

Values of parameters with a normal distribution were presented as a mean ± standard deviation, whereas values with non-normal distributions were expressed as median and range. In order to compare both groups, Student's *t*-test and the Mann-Whitney test were used, depending on the parameter distribution. χ^2 test was used to compare qualitative variables in contingency tables. The correlation between the statistically significant parameters for both groups and the parameter indicating the LV diastolic dysfunction (EmLV < 8 cm/s) has been also presented. Pearson's or Spearmans's correlation tests were used for correlation between variables. Receiver operating characteristic (ROC) analysis curves served to determine the optimal cutoff points for identifying patients with LV diastolic dysfunction.

In order to determine the diagnostic value of the evaluated parameters, univariate and multivariate logistic regression was employed. To assess the diagnostic value, odds ratio for particular

laboratory and echocardiographic parameters were calculated. In the analysis, the parameters were treated either continuously or dichotomously using their values as determined in the ROC analysis. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using STATISTICA 6 software.

All patients consented in writing for the inclusion in the research. The authors of this manuscript declare that they have complied with the Principles of Ethical Publishing present in the Declaration of Helsinki and that the study protocol was approved by a local ethics committee. The study protocol was approved by the Bioethics Committee (no 555/2011).

Results

The study group consisted of 50 patients with CKD, stages 2–5. CKD etiology in the study group included: hypertensive and ischemic nephropathy in 24 patients, glomerulonephritis in 5 patients, interstitial nephritis in 4 patients, diabetic nephropathy in 1 patient, polycystic kidney disease in 5 patients, autoimmune disease in 1 patient, whereas unknown etiology was present in 10 cases. Eight patients had stage 2 CKD (eGFR 89–60 mL/min), 24 patients had stage 3 CKD (eGFR 59–30 mL/min), 14 patients – stage 4 CKD (eGFR 29–15 mL/min), and 4 patients – stage 5 CKD (eGFR < 15 mL/min).

Patients were divided into 2 groups depending on their EmLV results. Group DD (+) consisted of 26 patients with LV diastolic dysfunction – EmLV < 8 cm/s, and group DD (–) comprised 24 patients with normal LV diastolic function, when EmLV ≥ ≥ 8 cm/s. Table 1 presents the clinical characteristics of both study groups.

Patients in both groups did not differ in age, sex, and presence of arterial hypertension, type 2 diabetes and CKD advancement.

There were no statistically significant differences between both groups regarding the frequency of taking allopurinol and another medications.

Results of laboratory tests and echocardiographic parameters for both groups are presented in Table 2.

Patients with LV diastolic dysfunction, as compared to patients with normal diastolic function, were characterized by significantly higher serum urea levels ($p = 0.044$) and serum UA levels ($p = 0.004$), and lower serum Ca levels ($p = 0.012$), whereas serum NT-proBNP obtained only the trend in the direction of significance, $p = 0.091$.

No differences were observed for the following parameters: the eGFR level and concentrations of creatinine, P, PLT, Hb and PTH.

In echocardiography, patients with LV diastolic dysfunction, as compared to patients with normal LV diastolic function, manifested higher values of IVSd ($p = 0.011$) and ratio of E/Em ($p = 0.002$), decreased early mitral flow velocity (E)

Table 1. General characteristics of both groups

Parameter	Total (n = 50)	DD (+) group (n = 26)	DD (–) group (n = 24)	p
Age (years)	65.2 ± 12.5	67 ± 12.7	63.2 ± 11.9	0.290
Sex (M/ F)	23/27	14/12	9/15	0.246
Diabetes n (%)	11 (22%)	6 (23%)	5 (21%)	0.848
Hypertension n (%)	40 (80%)	22 (85%)	18 (75%)	0.395
Stage 2 CKD	8 (16%)	3 (12%)	5 (21%)	0.370
Stage 3 CKD	24 (48%)	12 (46%)	12 (50%)	0.785
Stage 4 CKD	14 (28%)	8 (31%)	6 (25%)	0.649
Stage 5 CKD	4 (8%)	3 (12%)	1 (4%)	0.337
Beta blockers	26 (52%)	14 (54%)	12 (50%)	0.785
ACE inhibitors	28 (56%)	15 (58%)	13 (54%)	0.801
AT_1 blockers	5 (10%)	2 (8%)	3 (12%)	0.571
Thiazide-like diuretics	29 (58%)	16 (62%)	13 (54%)	0.597
Loop diuretics	4 (8%)	3 (12%)	1 (4%)	0.337
Ca blockers	21 (42%)	10 (38%)	11 (46%)	0.597
Statins	19 (38%)	11 (42%)	8 (33%)	0.513
Allopurinol	12 (24%)	4 (15%)	8 (33%)	0.137

DD (+) – group with diastolic dysfunction, DD (–) – group without diastolic dysfunction, M – male, F – female, CKD – chronic kidney disease, ACE – angiotensin – converting enzyme, AT_1 – angiotensin receptor A1, Ca – calcium.

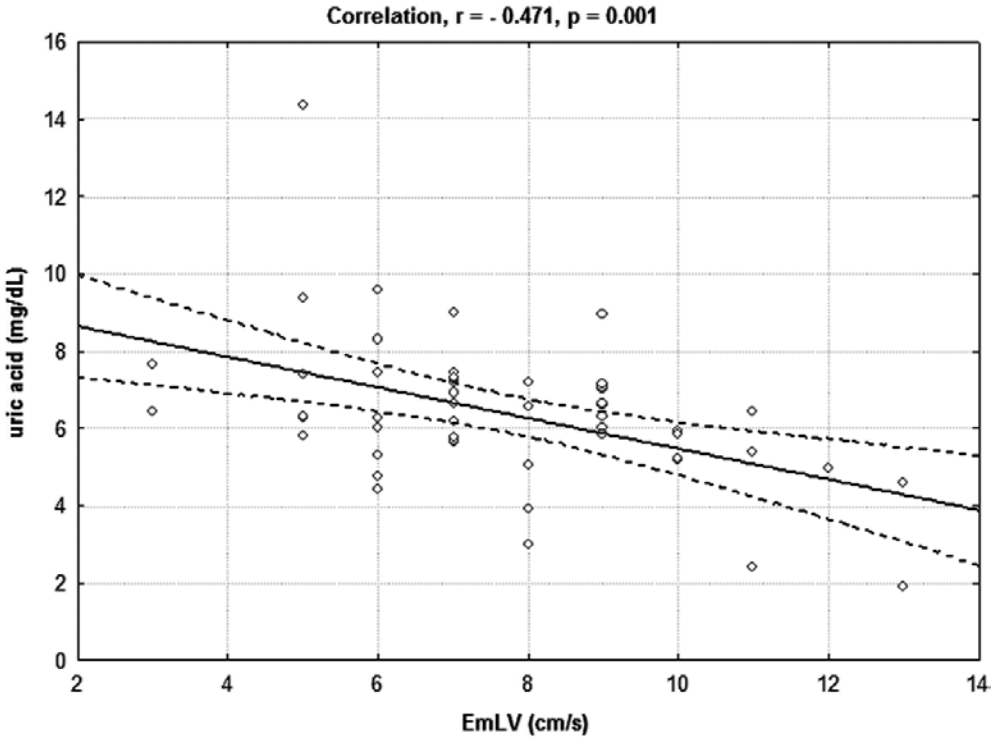

Fig. 1. Correlation between serum uric acid (UA) level and peak mitral annular early diastolic velocity (EmLV)

(p = 0.01), mitral flow E/A ratio (p = 0.003), SmLV (p = 0.003), EmLV (p < 0.0001) and Em/AmLV ratio (p < 0.0001). Patients in both groups did not differ as regards LVEDD, RVEDD, LAD, LVPWd, LVEF, LVMI, DT and AmLV.

ROC Analysis

The area under the ROC curve of serum UA level for the detection of LV diastolic dysfunction was 0.734, 95% CI (0.590–0.849), p = 0.001. The optimal cut-off value in the ROC analysis for UA was 6.0 mg/dL. This value was characterized by the sensitivity of 76.9% for diagnosing LV diastolic dysfunction and specificity of 62.5%; positive predictive value (PPV) was 69% and negative predictive value (NPV) 71%.

The area under the ROC curve of Ca level for the detection of LV diastolic dysfunction was 0.701 with 95% CI (0.553–0.823), p = 0.008. The optimal cut-off value in the ROC analysis for Ca was 9.82 mg/dL. For this value, sensitivity and specificity for diagnosing diastolic dysfunction amounted to 88% and 50%, respectively, PPV and NPV were 64.7%, and 80%, respectively.

Correlation Analysis

Correlation analysis demonstrated a statistically significant negative correlation between serum UA level and EmLV, r = –0.471, p = 0.001 (Fig. 1).

Univariate Logistic Regression

In order to determine the diagnostic value of laboratory and echocardiographic parameters univariate logistic regression analysis was performed and odds radio was calculated (Table 3).

Multivariate Logistic Regression

Using stepwise regression, we created a useful model for the diagnosis of LV diastolic dysfunction in CKD patients. Only those parameters with p < 0.1 in univariate logistic regression were considered (Table 4).

Among the examined parameters, only an increased serum UA level and lowered serum Ca level were found to be an independent predictive factors for LV diastolic dysfunction (p = 0.006 and p = 0.005, respectively). Other parameters did not reach statistical significance in multivariate analysis.

Discussion

The relationship between hyperuricemia and poor prognosis of patients with CHF is well documented [3, 16–18]. The other studies have shown that an elevated serum UA level was an independent predictor for the survival of patients with pulmonary arterial hypertension [19, 20]. In our study the CKD patients had normal tricuspid regurgitation pressure gradient in echocardiographic

Table 2. Characteristics of biochemical and echocardiographic parameters of patients from both groups

Parameter	Total (n = 50)	DD (+) group (n = 26)	DD (–) group (n = 24)	p
Creatinine (mg/dL)	1.49 (0.68–6.31)	1.54 (0.89–6.31)	1.42 (0.68–4.2)	0.165
eGFR (mL/min/1.73 m^2)	40.2 ± 20.9	36.4 ± 19.5	44.2 ± 22.0	0.192
Urea (mg/dL)	54 (19–204)	59 (26–163)	48 (19–204)	0.044
P (mg/dL)	3.7 (2.2–6.8)	3.8 (2.2–6.8)	3.6 (2.3–5.7)	0.337
Ca (mg/dL)	9.3 ± 0.9	9.0 ± 0.9	9.6 ± 0.9	0.012
Uric acid (mg/dL)	6.3 (1.9–14.3)	6.7 (4.4–14.3)	5.8 (1.9–8.9)	0.004
PLT (1000/uL)	219 ± 73	220 ± 89	218 ± 53	0.907
Hb (g/dL)	13.1 (7.7–16.6)	13.0 (8.7–16.60	13.3 (7.7–15.5)	0.298
PTH (pg/mL)	79 (24–346)	89 (29–346)	57 (24–326)	0.173
NT-proBNP (pg/mL)	205 (11.7–4967)	234 (32.6–4967)	145 (11.7–719)	0.091
LVEDD (cm)	4.7 ± 0.5	4.7 ± 0.6	4.7 ± 0.4	0.958
RVEDD (cm)	2.7 ± 0.2	2.7 ± 0.2	2.7 ± 0.2	0.955
LAD (cm)	4.1 ± 0.5	4.2 ± 0.5	4.0 ± 0.4	0.348
IVSd (cm)	1.1 (0.9–1.5)	1.2 (1.0–1.5)	1.1 (0.9–1.5)	0.011
LVPWd (cm)	1.1 (0.9–1.4)	1.2 (0.9–1.4)	1.1 (0.9–1.3)	0.070
LVEF (%)	59.0 (50–71)	58 (50–71)	60 (51–69)	0.251
LVMI (g/m^2)	96.6 (60.2–210.1)	103.6 (60.2–210.1)	88.3 (64.0–165)	0.101
E (cm/s)	63 ± 15	58 ± 12	69 ± 16	0.010
A (cm/s)	79 ± 17	82 ± 16	77 ± 17	0.257
DT (ms)	209 (101–352)	211 (133–352)	205 (101–303)	0.505
E/A ratio	0.74 (0.42–1.65)	0.67 (0.42–1.33)	0.87 (0.59–1.65)	0.003
SmLV (cm/s)	8 (5–14)	7 (5–14)	8 (7–11)	0.003
EmLV (cm/s)	7 (3–13)	6 (3–7)	9 (8–13)	< 0.0001
AmLV (cm/s)	10 ± 2.5	10 ± 2.6	10 ± 2.6	0.954
Em/AmLV	0.75 (0.37–2.0)	0.58 (0.37–1.16)	0.95 (0.5–2.0)	< 0.0001
E/Em ratio	8.6 (4.9–13.8)	9.0 (6.2–13.8)	6.6 (4.8–10.5)	0.002

DD (+) – group with diastolic dysfunction, DD (–) – group without diastolic dysfunction, eGFR – estimated glomerular filtration rate, P – serum levels of phosphorus, Ca – serum levels of calcium, PLT – platelets, Hb – haemoglobin, PTH – parathormone, NT-proBNP – N-terminal pro brain natriuretic peptide, LVEDD – left ventricular end-diastolic dimension, RVEDD – right ventricular end-diastolic dimension, LAD – left atrial diastolic dimension, IVSd – interventricular septal diastolic diameter, LVPWd – left ventricular left ventricular posterior wall dimension at diastole, LVEF – left ventricular ejection fraction, LVMI – left ventricular mass index, E – early transmitral peak velocity, A – late transmitral peak velocity, DT – deceleration time, E/A ratio – ratio of early transmitral peak velocity to late transmitral peak velocity, SmLV – peak mitral annular systolic velocity, EmLV – peak mitral annular early diastolic velocity, AmLV – peak mitral annular late diastolic velocity, Em/AmLV – ratio of peak mitral annular early diastolic velocity to peak mitral annular late diastolic velocity, E/Em ratio – ratio of early transmitral peak velocity to peak mitral annular early diastolic velocity.

examinations. Many studies have confirmed that UA through direct effect on inflammation, endothelial dysfunction, impaired nitric oxide (NO), the activation of RAAS negatively impact the course of both cardiovascular and kidney diseases [21–24]. These studies highlighted the importance of same hyperuricemia in the pathogenesis cardiovascular complications. However, other studies drew attention to the xanthine oxidase and its role in the mechanism of adverse events. Increased activity of this enzyme, which is involved in the reaction of hypoxanthine and xanthine to UA, causes the release of free radicals and increased oxidative stress [25–27]. Many studies have shown that patients with CHF and CKD receiving treatment with xanthine oxidase inhibitor allopurinol or oxypurinol were characterized by a better prognosis than patients without such treatment [28, 29]. In this group of patients with good effect xanthine oxidase inhibitors could probably results from the improvement endothelial function and reduced vascular oxidative stress than to decrease UA levels. Still other controversial appear in patients with CKD who have elevated levels of UA due to both the increased production and reduced excretion by kidney damage. In some studies hyperuricemia

Table 3. Evaluation of potential predictive factors for LV diastolic dysfunction (EmLV < 8 cm/s) in univariate logistic regression

Parameter	Odds Ratio	95% CI	p
Creatinine (mg/dL)	1.40	0.78–2.51	0.233
eGFR (mL/min/1.73 m^2)	0.98	0.95–1.01	0.191
Urea (mg/dL)	1.01	0.99–1.02	0.109
P (mg/dL)	1.17	0.65–2.10	0.577
Ca (mg/dL)	0.41	0.19–0.89	0.020
Ca ≤ 9.82 mg/dL	7.33	1.65–32.4	0.007
Uric acid (mg/dL)	1.92	1.14–3.23	0.012
Uric acid > 6.0 mg/dL	5.88	1.59–21.6	0.006
PTH (mg/dL)	1.00	0.99–1.01	0.392
Log_{10} NT-proBNP (pg/mL)	3.53	0.88–14.1	0.068
IVSd (cm)	168.9	2.11–13510	0.020
LVPWd (cm)	106.4	0.57–19885	0.070
LVMI (g/m^2)	1.01	0.99–1.04	0.091

CI – confidence interval, eGFR – estimated glomerular filtration rate, P – serum levels of phosphorus, Ca – serum levels of calcium, PTH – – parathormone, NT-proBNP –N-terminal pro brain natriuretic peptide, IVSd – interventricular septal diastolic diameter, LVPWd – left ventricular posterior wall dimension at diastole, LVMI – left ventricular mass index.

Table 4. Assessment of independent predictive factors for LV diastolic dysfunction (EmLV < 8 cm/s) in multivariate logistic regression

Parameter	Odds Ratio	95% CI	p
Urea (mg/dL)	1.00	0.98–1.03	0.746
Ca (mg/dL) ≤ 9.82 mg/dL	26.4	2.44–286.2	0.005
Uric acid > 6.0 mg/dL	14.3	2.0–103.2	0.006
Log_{10} NT-proBNP (pg/mL)	1.50	0.15–14.3	0.714
IVSd (cm)	2.51	0.001–6879	0.814
LVPWd (cm)	1.02	0.0001–317972	0.997
LVMI (g/m^2)	1.01	0.98–1.05	0.400

CI – confidence interval, Ca – serum levels of calcium, NT-proBNP – N-terminal pro-brain natriuretic peptide, IVSd – interventricular septal diastolic diameter, LVPWd – left ventricular left ventricular posterior wall dimension at diastole, LVMI – left ventricular mass index.

was an independent predictor of increased mortality only in patients with CKD [30, 31], in other studies this was found only in patients with normal renal function [25, 32]. Most of these trials evaluated the impact of hyperuricemia on the prognosis patients, the rate of hospitalizations and occurrence of adverse events. However, direct assessment of influence hyperuricemia in left ventricular diastolic dysfunction is until poorly understood. In our study among patients with CKD we found that an independent predictor factor of LV diastolic dysfunction was an elevated concentration of UA in the blood serum of > 6.0 mg/dL with HR = 14.3 (95% CI 2.0 – 103.2), p = 0.006. In addition to elevated levels of UA, reduced concentration of serum Ca level was also an independent predictor, which confirms our previous study [33]. Cicoira M et al. [8] presented the relationship between LV diastolic dysfunction which was defined as restrictive mitral filling pattern and elevated UA levels. Patients with CHF with mitral inflow restriction, defined as the E/A > 2 or E/A > 1 and DT < 140 ms, as compared to patients without restriction dysfunction characterized by significantly higher levels of UA (0.48 ± 0.14 mmol/L vs 0.38 ± 0.08 mmol/L, respectively, p < 0.001). It was also demonstrated that there is a positive correlation between serum UA with the parameters of pulsed Doppler mitral flow (E,E/A and DT). The study Krishnan E et al. [9] in 2269 patients without CHF of the Framingham Heart Study elevated the effect of UA in the presence of future subclinical HF. The authors showed that, when patients were analyzed according to serum UA quartiles, those in the highest quartile (6.0–10.35 mg/dL serum UA) had a significantly a higher LV wall thickness, LV end-diastolic diameter and LV mass compared with those in the lowest quartile (1.2–4.2 mg/dL). They have also found that hyperuricemia can be a marker for subsequent LV dysfunction. The relationship between hyperuricemia and LV dysfunction was evaluated by Tavil Y et al. [34]. In this study, the authors assessed the LV myocardial performance index (LV MPI) in tissue Doppler imaging in patients with arterial hypertension (AH) with and without hyperuricemia and a group of healthy control volunteers. Obviously LV MPI was damaged in groups with AH with and without hyperuricemia compared to controls (0.53 ± 0.07, 0.48 ± 0.09, and 0.39 ± 0.07, respectively, p < 0.001). However, it was also observed that the value of LV MPI in patients with AH and hyperuricemia was significantly higher than in patients with AH without hyperuricemia [34].

In our opinion, hyperuricemia can play an important role in the development of diastolic dysfunction in patients with CKD. We believe that harmful effects on the heart may be due to both the increased activation of xanthine oxidase and with increased levels of UA in the serum against damaged kidneys. It is difficult to explain why the NT-proBNP was not an independent predictor of diastolic dysfunction among our patients with CKD. Many previous studies have confirmed the importance of NT-proBNP in the diagnosis of systolic and diastolic CHF and the prognosis of patients with CHF and CKD [35, 36]. In order to evaluate the role of UA in the development of LV diastolic dysfunction, there is a need for further study.

Limitations of this study include a small, one--center study group; secondly, only a single UA measurement was performed, and we know that it may not accurately assess hyperuricemia because many factors, including exercise, diet, drugs and state of hydration, may result in transient fluctuations in serum UA levels.

The authors concluded that hyperuricemia is an independent predictive factor for left ventricular diastolic dysfunction in patients with chronic kidney disease. Further studies with a larger number of patients are necessary to confirm these findings and the clinical implications.

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