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Original Article *Özgün Araştırma*

HYPERURICEMIA IN DIALYSIS PATIENTS AND ITS ASSOCIATION WITH LEFT VENTRICULAR MASS INDEX

Diyaliz Hastalarında Hiperürisemi ve Sol Ventrikül Kitle İndeksi ile İlişkisi

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ABSTRACT

Objective: Hyperuricemia leads to endothelial dysfunction and vascular stiffness; however, there are not enough studies on the effect of uric acid levels on the myocardium in pediatric dialysis patients. In this study, we aimed to investigate the relationship between uric acid levels and ventricular hypertrophy in children undergoing dialysis.

Material and Methods: This multicenter retrospective study was conducted among nine centers. We retrospectively reviewed the medical records of pediatric long-term dialysis patients.

Results: One hundred and thirty-one patients were enrolled in this study. The mean age was 11.7±5.0 years (range 1-19.5) (M/F=68/63). One hundred and seven patients were undergoing peritoneal dialysis (PD) and 24 patients were on hemodialysis (HD). The mean left ventricular mass index (LVMI), and the percentage of patients with left ventricular hypertrophy (LVH) were significantly higher in the hyperuricemia group (56±24 vs 42±14 g/m$^{2.7}$, p=0.001; 63.3% vs 41.9 %, p<0.001 respectively) than the normal uric acid (UA) group. The mean potassium level was significantly higher (4.6±0.6 vs 4.3±0.6 mEq/L, p=0.004), and hemoglobin lower (10.2±1.3 vs 10.9±1.0 g/dl, p=0.001) in patients with left ventricular hypertrophy than without left ventricular hypertrophy. Seven patients (9.2%) died in the hyperuricemia group, and 1 (1.8%) in the latter group. The multivariate regression analysis showed that hyperkalemia was the only parameter associated with left ventricular hypertrophy (OR:0.931, CI: 95%, 0.886-7.269, p= 0.043).

Conclusion: Hyperuricemia and hyperkalemia seemed to be associated with left ventricular hypertrophy. So uric acid and potassium lowering medical treatment and dietary interventions may be considered essential for decreasing cardiac morbidity in pediatric long-term dialysis patients.

Keywords: *Dialysis, hyperuricemia, hyperkalemia, left ventricular hypertrophy*

ÖZ

Amaç: Hiperüriseminin, endotel işlev bozukluğuna ve damar sertliğine yol açtığı bilinmektedir ancak çocukluk çağında diyaliz hastalarında kandaki ürik asit seviyelerinin miyokard üzerindeki etkisi konusunda yeterli çalışma bulunmamaktadır. Bu çalışmada, diyalize giren çocuk hastalardaki ürik asit düzeyinin ventriküler hipertrofi ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışma, 9 merkezin katıldığı çok merkezli bir retrospektif çalışma niteliği taşımaktadır. Bu merkezlerde takip edilen çocuk yaştaki diyaliz hastalarının tıbbi kayıtları retrospektif olarak incelendi.

Bulgular: Bu çalışmaya 131 hasta dâhil edildi. Ortalama yaş 11,7±5,0 yıl (1-19,5 arası) olan hastaların (E/K=68/63). 107'si periton diyalizi, 24'ü ise hemodiyaliz programında idi. Hiperürisemi grubunda olan hastaların, ortalama sol ventrikül kütle indeksi ve sol ventrikül hipertrofisi olanların oranı normal ürik asit grubuna göre anlamlı olarak daha yüksekti (sırasıyla 56±24 vs 42±14 g/m$^{2.7}$, p=0,001; %63,3 vs %41,9, p<0,001). Sol ventrikül hipertrofisi olan hastalarda ortalama potasyum düzeyi, hipertrofisi olmayanlara göre olarak anlamlı şekilde daha yüksekti (4,6±0,6 vs 4,3±0,6 mEq/L, p=0,040). Ortalama hemoglobin düzeyi de hipertrofik grupta anlamlı olarak daha düşüktü (10,2±1,3 vs 10,9±1,0 g/dl, p=0,001). Hiperürisemi grubunda 7 hasta (%9,2) hayatını kaybederken, bu sayı normal ürik asit grubuna 1 (%1,8) idi. Çoklu regresyon analizi, hiperkaleminin sol ventrikül hipertrofisi ile ilişkili olan tek parametre olduğunu gösterdi (OR:0,931, CI: 95%, 0,886-7,269, p= 0,043).

Sonuç: Sonuçlarımız, diyaliz hastalarında sol ventrikül hipertrofisi oluşum ve gelişmesinde, hiperürisemi ve hiperkaleminin rolü olabileceğini göstermektedir. Bu nedenle, bu hastalarda kardiyak morbiditenin azaltılması için hastalara ürik asit ve potasyum düşürücü tıbbi tedaviler verilerek beraberinde sıkı diyet kısıtlaması yapılmalıdır.

Anahtar Kelimeler: *Diyaliz, hiperürisemi, hiperkalemi, sol ventrikül hipertrofisi*

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INTRODUCTION

Hyperuricemia is frequently seen in children with chronic kidney disease (CKD) as a result of decreased uric acid (UA) excretion from the kidneys due to impaired renal function.[1] Cardiovascular complications are the leading factors contributing to mortality in CKD patients.[2] Left ventricular hypertrophy (LVH) is a well-known outcome for pediatric patients treated by long-term dialysis.[3] Previous studies showed an association between hyperuricemia and cardiac disease. Kleber found an association between hyperuricemia and coronary artery disease, peripheral vascular disease, cardiomyopathies, and hypertension.[4] Silbernagel et al. showed a significant correlation between hyperuricemia and cardiovascular mortality.[5] Hyperuricemia is also a component of metabolic syndrome in children with insulin resistance and LVH is much more common among these patients.[6-8]

The effect of UA levels in long-term dialysis patients on the myocardium is not clear. The Guidelines of the European Society of Cardiology/European Society of Hypertension have introduced that high UA constitutes a noteworthy risk factor for cardiovascular morbidity.[9] Hyperuricemia leads to endothelial dysfunction, vascular stiffness, and ultimately to LVH.[10] Adewuya et al. showed in hypertensive adult patients that high serum UA was associated with increased LV mass index (LVMI) and it was a predictor of cardiovascular morbidity.[11] However, there are conflicting results regarding the effect of anti hyperuricemic treatment on CKD progression.[12] Accordingly, the primary aim of this study was to examine the potential correlation between UA levels and left ventricular hypertrophy in pediatric patients undergoing prolonged dialysis.

MATERIALS AND METHODS

We carried out a retrospective analysis of medical records of children undergoing prolonged dialysis in this study. The study included individuals who commenced dialysis between 2008 and 2013 and had undergone an echocardiographic assessment within the three months preceding the data collection date. Participants excluded from the study were those aged below 20 and individuals who had been on dialysis for fewer than three months. Demographic findings, data on long-term dialysis modalities, laboratory tests, blood pressure measurements, mean arterial pressures (MAP), body mass index (BMI), standard deviation scores (SDS) of BMI and MAP were noted. Values of laboratory parameters recorded on a monthly basis over the past year were noted and time-averaged (T-A) levels were calculated. Hypertension was defined according to the last guidelines.[13] We calculate the mean of three measurements of systolic and diastolic blood pressure for each patient. Mean arterial pressure is a measure of the average arterial pressure during a cardiac cycle and in medical practice, MAP is often used as an indicator of perfusion pressure and overall cardiovascular health. We calculated the MAP by using the formula: MAP= systolic blood pressure + 2 x diastolic blood pressure /3.[14] Anemia is defined as Hb value less than the 5th percentile for age and sex.[15] Hypoalbuminemia was defined as an albumin level of less than 3.5 g/dl.[16] Finally, metabolic acidosis is defined as consistently low bicarbonate levels in the blood, typically measuring less than 22 mEq/L.[17]

Echocardiographic data, specifically regarding LVMI and LVH, were gathered. These examinations took place on weekdays at all centers, occurring between two dialysis sessions for HD patients and for PD patients with an empty abdomen. The criteria for determining LVMI and LVH adhered to the guidelines set by the American Society of Echocardiography.[18] The calculation of left ventricular mass followed the Devereux.[19,20] Left ventricular hypertrophy was defined using the LVM index exceeding the 95th percentile, as per the methodology outlined in Foster BJ et al.[21]

The patients were divided into subgroups by UA level, formed by the pediatric reference values of the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) project study) as hyperuricemia and normal UA groups.[22]

Statistical analysis

To compare continuous variables between the two groups, Student's t-test was employed, while differences in proportions were assessed using the chi-square test. Correlations between parameters were examined using Pearson/Spearman correlation tests. Regression analysis was utilized to evaluate the relationship between left LVH and factors such as UA, electrolytes, BMI, BMI SDS, MAP, MAP SDS, residual urine volume, and CRP. The Ethics Committee of Gazi University Faculty of Medicine (Decision no: 302) approved the study.

RESULTS

One hundred and thirty-one patients were enrolled in this study. The mean age was 11.7±5.0 years (range 1-19.5) (M/F=68/63). One hundred and seven patients were undergoing peritoneal dialysis (PD) and 24 patients were on hemodialysis (HD). The mean LVMI of all patients was 58±31 (21-215) g/m$^{2.7}$. The mean LVMI was 74.2±30.4 g/m$^{2.7}$ in 81 patients with LVH and 33.2±4.7 g/m$^{2.7}$ in 50 patients without LVH ($p<0,001$).

The mean UA levels were significantly different between hyperuricemia and normal UA groups (5.7±0.9 mg/dl and 4.8±0.7 mg/dl, $p<0.001$). The percentage of females was significantly greater in the hyperuricemia group (63.3% vs 27.9%, $p\leq0.001$).

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Patients with hyperuricemia were younger (9.7±5.0 years vs 14.6±3.5, p<0.001). The BMI was lower and PTH level was higher in the hyperuricemia vs normal UA group (16.1±2.1 vs 17.4±3.1, p=0.023; 437±65 vs 398±75 pg/ml, p=0.026 respectively). The mean LVMI and the percentage of patients with LVH were significantly higher in the hyperuricemia group (56±24 vs 42±14 g/m$^{2.7}$, p=0.001; 63.3% vs 41.9 %, p<0.001 respectively) than the normal UA group. There was no difference in mean values of mean arterial pressure, Hb, albumin, bicarbonate, CRP, creatinine, and eGFR between hyperuricemia and normal UA groups (Table 1). Seven patients (9.2%) died in the hyperuricemia group, and 1 (1.8%) in the other group.

The UA levels, LVMI, and the percentage of patients with LVH were significantly higher in HD patients in comparison to PD patients (Table 2).

Table 1: Comparison of laboratory data in long-term dialysis patients by uric acid groups

Parameters	Hyperuricemia n= 76	Normal uric acid n= 55	p
Female n (%)	48 (63.3)	15 (27.9)	<0.001
BMI (kg/m^2)	16.1±2.1	17.4±3.1	0.023
Uric acid (mg/dl)	5.7±0.9	4.8±0.7	<0.001
Age (years)	9.7±5.0	14.6±3.5	<0.001
Mean arterial pressure (mmHg)	83±18	86±17	0.498
Residual urine volume (ml/m^2)	450±106	545±95	0.508
Creatinine (mg/dl)	7.5± 2.5	6.5 ± 2.4	0.052
eGFR (mL/min/1.73 m^2)	8.2±3.3	8.6±3.1	0.638
BUN (mg/dl)	58.6 ± 23.0	49.1 ± 19.2	0.026
Hemoglobin (g/dL)	10.41±1.33	10.77±1.20	0.155
Frequency of anemia	83.3	88.4	0.377
Ferritin (ng/ml)	457±71	373±40	0.312
Albumin (gr/dl)	3.3±0.8	3.5±0.5	0.348
Frequency of hypoalbuminemia	10.0	9.3	0.592
Parathormone(pg/ml)	437±65	398±75	0.026
Calcium (mg/dl)	9.3±0.6	9.2±0.6	0.504
Phosphate (mg/dl)	5.6±1.1	5.3±0.7	0.201
Sodium (mEq/l)	136.8±3.1	137.2±2.9	0.449
Potassium (mEq/l)	4.5±0.6	4.3±0.6	0.130
CRP (mg/L)	1.3±0.2	1.2±0.3	0.909
Bicarbonate (mEq/l)	22.8±2.4	23.3±1.8	0.253
Frequency of metabolic acidosis	11.7	4.7	0.159
Left ventricular mass index (g/m$^{2.7}$) n= 131 patients	56±24	42±14	0.001
Patients with left ventricular hypertrophy (%) n= 131 patients	63.3	41.9	0.031
Number of deaths (%)	9.2	1.8	0.128

Table 2: Comparison between dialysis modalities regarding uric acid and LVMI

Parameters	PD (N=107)	HD (N=24)	P
Mean uric acid level (mg/dl)	5.2 ± 0.8	5.8 ± 1.3	0.021
Patient with normal uric acid level (%)	45.2	26.3	0.131
Mean left ventricular mass index (g/m$^{2.7}$) Total patients: 131*	47 ± 19	68 ± 26	0.003
Patients with left ventricular hypertrophy (n (%)	57 (53.2)	21 (87.5)	<0.001

The mean potassium level was significantly higher (4.6±0.6 vs 4.3±0.6 mEq/L, p=0.04), and the hemoglobin level was lower (10.2±1.3 vs 10.9±1.0 g/dl, p=0.001) in patients with LVH than without LVH. On the other hand, there was no significant difference in other electrolytes including sodium, calcium, and phosphate.

There was no correlation between UA level and LVMI, creatinine, mean arterial pressure or urine output. Uric acid level was negatively correlated with Hb (p=0.002, r=-0.243) and positively correlated with ferritin, (p=<0.001, r=0.324), phosphate (p=0.015, r=0.194), potassium (p=0.036, r=0.166) and PTH (p=0.023, r=0.181).

The univariable analyses using the above-identified parameters showed that high uric acid level, high BMI, low mean residual volume, hypocalcemia, hyperkalemia, high PTH, and high CRP were risk factors for high LVMI (p<0.05) (Table 3). The multivariate regression analysis showed that hyperkalemia was the only parameter associated with LVH ((OR:0.931, CI: 95%, 0.886-7.269, p= 0.043).

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Table 3: Univariate and multivariate regression analysis in the long-term dialysis patients for high LVMI

	Odds ratio	Lower level	Upper level	P
Univariate analysis				
Uric acid level	0.161	-0.759	7.959	**0.104***
Mean arterial pressure	0.008	0.986	1.031	0.477
BMI	-0,137	0.745	1.021	**0.089**
Residual urine volume	-0.229	-8.891	-0.587	**0.026**
Creatinine	-0.52	-0.707	0.383	0.557
Hemoglobin	-0.72	-3.094	1.303	0.422
Ferritin	0.218	0.04	0.30	**0.012**
Albumin	-0.073	-10.627	4.392	0.413
Calcium	-0.160	-11.761	1.167	**0.107***
Phosphate	-0.015	-4.623	3.970	0.881
Sodium	0.010	-1.350	1.499	0.918
Potassium	0.270	2.697	15.607	**0.006**
Parathormone	0.278	0.007	0.031	**0.001**
CRP	0.565	4.221	8.095	**<0.001**
Bicarbonate	-0.149	-3.447	0.419	0.124
Multivariate analysis				
Uric acid level	0.161	0.558	2.473	0.671
BMI	-0.255	0.571	1.053	0.103
Residual urine volume	-0.181	0.453	1.538	0.562
Parathormone	0.001	0.997	1.004	0.716
Calcium	-0.557	0.193	1.706	0.317
Potassium	0.931	0.886	7.269	**0.043**
CRP	0.863	0.585	9.607	0.227

*<0.200 (if p value <0.200, this variable is included in multivaraite analysis)

DISCUSSION

This study demonstrated that hyperuricemic pediatric long-term dialysis patients have higher LVMI, higher LVH prevalence and higher death rates. There was a female preponderance in the hyperuricemia group. Hoieggen et al. showed that the relation between serum UA and cardiovascular events was stronger in females than in males in patients with LVH.[23] We proposed that hyperuricemia especially in females should be intervened without delay.

Studies have indicated that serum urate levels in females are lower than in males during and after adolescence period, likely due to higher renal clearance of urate in women, which may be attributed to their elevated plasma estrogen levels in healthy individuals.[24] However, this effect was absent in our study population with nonfunctional kidneys.

Chen et al. showed an association between UA and LVMI in 540 adult patients with CKD.[25] They suggested that UA was independently associated with LVMI and these variables were risk factors for progression to kidney failure. Although the mechanism of the association between UA and LVH has yet to be known, previous studies showed that hyperuricemia contributes to an increase in tumor necrosis factor-alpha, stimulates mitogen-activated protein kinases, triggers renin and angiotensin secretion, and enhances oxidative stress. These factors collectively culminate in cardiac hypertrophy.[26] Experimental and in vitro studies showed that detrimental mechanisms of hyperuricemia including inflammation, endothelial cell dysfunction, and vascular smooth muscle cell proliferation subsequently result in cardiac hypertrophy.[27] In line with previous studies, we found that the LVMI was notably higher in the hyperuricemia group when compared to the group with normal UA levels.[28] However, there was no correlation between LVMI and UA level. Additionally, a recent randomized trial clearly showed that anti hyperuricemic treatment did not decrease the progression of CKD.[12] In our study, univariate and multivariate analysis showed that hyperuricemia was not predictive of high LVMI. Different observations related to the regression analysis of UA may be caused by the confounding effect of CKD. Moreover, employing a lower cutoff (as in the CALIPER study) to define hyperuricemia may have introduced a potential bias, as it could lead to the selection of a population with only minimal elevation in UA levels and, consequently, a significantly lower risk profile.

Interestingly, in our study, multivariate Cox regression analysis revealed that hyperkalemia emerged as an independent predictor of LVH. Additionally, the mean potassium level was higher in the hyperuricemia group but it was not statistically significant. Long-term dialysis induces a decrease in plasma potassium concentrations.[29] The mean potassium level of the patients with LVH was relatively high. We believe that

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this result was related to the high rate of ACE inhibitor use in hypertensive patients, especially in the LVH group. However, this hypothesis is not supported by sufficient evidence. So randomized controlled studies are needed to prove it. A previous study showed a positive correlation between aldosterone and LVMI.[30] We hypothesized that high aldosterone levels induced by high potassium levels will lead to LVH. Prospective studies are needed to determine this effect in CKD patients. So effective interventions for controlling hyperkalemia, either dietary restriction or potassium-lowering treatment may be valuable to prevent LVH. Moreover providing a relatively lower potassium level might be preferred in pediatric long-term dialysis patients. New drugs, such as patiromer and sodium zirconium cyclosilicate have newly been introduced. Patiromer effectively captures potassium within the digestive system and decreases serum potassium and aldosterone concentrations, regardless of plasma renin activity, among individuals with CKD.[31,32]

All of the studies aforementioned were conducted in adults, mainly in elderly patients. From this point our study is original. So our result suggests that to postpone and also to prevent cardiac hypertrophy, strict dietary counseling and medical management are of particular importance in CKD cases with hyperuricemia and hyperkalemia.

Anemia and hyperuricemia are two important complications of CKD.[33] We found a negative correlation between these two variables which was shown previously in CKD patients.[34]

The association of hyperphosphatemia with vascular dysfunction in CKD patients suggests a relationship between high phosphate and LVH and experimental studies support this hypothesis.[35] Foley et al. showed in young adults that phosphate level was associated with LVH. Moreover, this association persisted after covariate adjustment.[36] On the other hand, the same researchers showed that hyperphosphatemia was a risk factor for left ventricular dilatation but not for LVH in long-term dialysis patients.[37] Although we found a positive correlation between phosphate and LVMI, the regression analysis did not show an association between phosphate and LVMI and also the presence of LVH. These results may be caused by the existence of multiple factors affecting both variables.

Many previous studies have shown a strong association of high BMI with elevated uric acid.[38,39] The fact that it was relatively low in the hyperuricemia group in our study suggests that this relationship may have been lost in dialysis patients.

There are some limitations in our study. It was not possible to homogenize the echocardiogram records, blood pressure information, and laboratory methodologies across nine different centers. This diversity in methodology could have potentially constrained the dependability of our outcomes. Lack of information on medication (steroids etc.) and the volume status were the other limitations. Additionally, the serum concentration of UA is also affected by insulin resistance and dyslipidemia, which were not analyzed in the current study, since our study was retrospective, we could not investigate insulin resistance, etc.[40] On the other side, the fact that 9 centers participated in the study adds further value to the article since such studies are rare in this age group in our country.

In conclusion, hyperuricemia and hyperkalemia seemed to be associated with LVH. So uric acid and potassium-lowering medical treatment and dietary interventions may be considered essential for decreasing cardiac morbidity in pediatric long-term dialysis patients. It would be suggested to conduct a similar study in pediatric patients with stage 3/4 CKD by removing dialysis-related factors.

Conflict of Interest: The authors have no conflicts of interest to declare.

*Contribution Statement***:** Concept/Planning: SAB, YK; Analysis/Interpretation: SAB, YK; Data Provision: SAB, YK, ES, AN, AKB, MT, SGÖ, GÖ, İD, CA, MA, YÖA., GP, BA, FLS; Writing: SAB, YK; Review and Editing: SAB, YK; Approval: SAB, YK

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