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Research Article

Correlation between endothelial dysfunction and left ventricular hypertrophy in children with initial stages chronic kidney disease

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Abstract. Objective: The aim was to study the correlation between inflammation, endothelial dysfunction and left ventricular hypertrophy in children with chronic kidney disease (CKD) stage 2 and 3. Material and methods. The study was conducted on 67 children aged between 6 -17 years. 47 patients had chronic pyelonephritis and CKD stage 2 or 3. The control group consisted of 20 healthy children. All patients underwent routine medical history taking, physical examination, ultrasound imaging and laboratory assessment. Results. Patients were divided into groups depending on the stage of CKD: group 1 included 30 patients with CKD stage 2, group 2 included 17 patients with CKD stage 3. Patients with CKD stage 3 had significantly lower growth rates ($p = 0.024$), body weight ($p = 0.031$) and hemoglobin ($p = 0.012$) compared with the control group. The systolic blood pressure ($p = 0.025$), the diastolic blood pressure ($p = 0.026$), and the uric acid ($p = 0.019$) in this group of patients were statistically higher compared with the control group. Both the patients of group 1 and group 2 had levels of C-reactive protein (CRP) and microalbuminuria significantly higher than those in control group. Patients with CKD stage 3 had an enlarged left ventricle, confirmed by a significant increase of the end-diastolic index (EDI) ($p = 0.011$) and the end-systolic index (ESI) ($p = 0.016$) compared with the control group. The left ventricular myocardial mass index (LVMI) was reliably higher in patients with both CKD stage 2 ($p = 0.025$) and CKD stage 3 ($p = 0.007$) compared with the control group. Left ventricular hypertrophy was found in 36.7% of the patients with CKD stage 2 and 47.0% of the patients with CKD stage 3. Endothelial dysfunction was detected in 90% of patients with CKD stage 2 and in 100% of patients with CKD stage 3. A significant negative correlation between levels of endotelium-dependent flow-mediated dilation (FMD) and LVMI ($r = -0.49$, $p = 0.031$), CRP ($r = -0.76$, $p < 0.001$), microalbuminuria ($r = -0.65$, $p < 0.001$) was found in all patients with CKD. Conclusions. Children with chronic pyelonephritis have early signs of endothelial dysfunction and systemic inflammation, which worsens during mild-to-moderate CKD progression. The presence of the reliable correlations between endothelial dysfunction, systemic inflammation and LVMI suggests the involvement of the endothelium in the development and maintenance of chronic inflammation and the left ventricular hypertrophy formation.

Key Words: chronic pyelonephritis, children, chronic kidney disease, endothelial dysfunction, left ventricular hypertrophy.

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Introduction

Chronic kidney disease (CKD) remains an important medical and social health problem, given the high prevalence and increased risk of mortality and morbidity (Rhee et al 2015). In patients with CKD, cardiovascular pathology is the most important cause of increased mortality and it directly affects the long-term survival (Fox et al 2012; Mahmoodi et al 2012). Similarly to adults, in paediatric patients with chronic renal failure, the association of cardiovascular diseases most often result in death (Mitsnefes et al 2013; Weaver et al 2017). In patients with CKD, cardiovascular complications are associated with traditional risk factors, such as left ventricular hypertrophy (LVH) (Matsushita et al 2017), as well as nontraditional risks such as anemia, calcification, hyperhomocysteinemia, vitamin D deficiency, insulin resistance and oxidative stress (He et al 2017; Mann et al 2015; Matsushita et al 2016; Matsushita et al 2014). There are studies that prove the decisive role of endothelial dysfunction in the development of atherosclerosis and vascular disorders associated with CKD (Satoh 2012; Shang et al 2017).

One of the mediators of endothelial dysfunction in patients with CKD is inflammation (Bernelot Moens et al 2017; Lilitkarntakul et al 2014). However, associations between inflammation, endothelial dysfunction and formation of cardiovascular complications have been insufficiently highlighted in pediatric patients with pre- dialysis CKD. In this work, we studied the correlation between inflammation, endothelial dysfunction and left ventricular hypertrophy in children with CKD stage 2 and 3.

Materials and methods

Patients, groups

We study 47 children (24 boys, 23 girls) aged from 6 to 17 years with chronic pyelonephritis (CP) and CKD 2 and 3 stages, who were subjected to inpatient treatment at the department of nephrology of "Dnipropetrovsk Regional Children's Clinical Hospital" DRC. The control group consisted of 20 healthy children. The

planned clinical trial was approved by the Bioethics Committee of the Dnipropetrovsk Medical Academy MOH of Ukraine and was carried out in compliance with the Helsinki Declaration guidelines (1975). All participants and / or their parents were fully informed about the methods and scope of the study and provided their written informed consent to participate.

Criteria for the patients inclusion into the study were as follows: the presence of voluntary informed consent of the child and her parents to participate in the clinical study; patients age from 6 to 17 years 11 months 29 days; the presence of a verified chronic pyelonephritis and CKD 2 and 3stages diagnosis; the absence of clinical and laboratory signs of chronic pyelonephritis exacerbation. Criteria for the patients exclusion from the study were: refusal of the child or his/her parents to participate in the clinical trial; the presence of congenital heart disease or other primary cardiac diseases, acute infections.

All patients underwent routine medical history taking, physical examination, ultrasound imaging and laboratory assessment. The examination was carried out during the remission period of chronic pyelonephritis, at least one month after the last exacerbation. The biochemical parameters (level of urea, creatinine, uric acid, electrolytes, albumin) necessary for determining the renal function status were determined. The velocity of glomerular filtration was calculated using the formula by Schwartz et al. Definition and classification of CKD stages were made using standard criteria (Stevens et al 2013). The level of C-reactive protein (CRP) was studied by means of the latex agglutination method using the "Granum" set of reagents (Ukraine). Microalbuminuria was determined by means of the "Micral-Test", Roche Diagnostics (Switzerland).

Ultrasound investigation

The ultrasound examination was carried out in a specially designed room (purpose-built room), where the air temperature is permanently maintained at 22-24oC. The test was carried out in the morning after 12-h overnight fasting. At least 12 hours before the study, patients avoided taking coffee and tea, performing physical exercises. 48 hours before the study all vasoactive medicines were discontinued. Patients were examined in a lying position after a 10-15 minute rest.

Endothelial function was evaluated by using digital ultrasonic diagnostic complex "Toshiba Xario (Japan)" using a 7.5 MHz sensor. We performed an ultrasound assessment of endotelium-dependent flow-mediated dilation (FMD) of the brachial artery and calculated the percentage of the increase in the diameter of brachial artery. The norm was an increase in FMD more than 10% (Celermajer 1998).

Echocardiography (EchoCG) to determine the presence of left ventricular (LV) hypertrophy (LVH) was carried out with "Acuson CV70" ultrasound scanner (Siemens) in 2D mode using the standard procedure. The main indices of systolic and diastolic function of the LV were determined, including end-diastolic index (EDI), end-systolic index (ESI), ejection fraction (EF), left ventricular relative wall thickness (LVRWT). The calculation of the LV myocardial mass

(LVM) and the myocardial mass index (LVMI) were performed. The LVM was calculated using the formula by Devereux and Reichek (Devereux 1977). The Z-scores of LVM were calculated according to the height (Foster et al 2008). The LVMI was obtained by dividing the LVMI by the height (mass [g] / height [m] 2.7) (de Simone et al 1992). for the normalizing and linearizing the correlation between LVM and the height. Lipid hypertrophy was determined when the LVMI was ≥ 95 percentiles for healthy children and adolescents (Khoury et al 2009). Since the LVMI that is indexed to the height does not completely take into account the changes due to growth, we also used Z-scores based on age and sex (Khoury et al 2009). Measurement of office blood pressure (OBP) was performed before the ultrasound examination after the patient's sitting for 10-15 minutes in a calm condition.

Statistical analysis

Statistical analysis was carried out using STATISTICA software for Windows version 8.0 (StatSoft, Tulsa, OK). Distribution of variables was tested with Shapiro-Wilk's test. Non-parametric variables are given as median (interquartile range) and percentage for categorical variables. The Kruskal–Wallis One Way Analysis of Variance (ANOVA) on Ranks (H) was used for testing a statistically significant difference in the median values among all groups. Significance point was defined using Bonferonni adjustment. To compare two independent samples non-parametric Mann-Whitney U-test was applied. The correlation between variables was assessed by Spearman correlation coefficient. The level of significance was set at 0.05.

Results

About 80.9% (38/47) of patients with chronic pyelonephritis had of organic urodynamics disorders (congenital anomalies of the kidneys and / or urinary tract), 19.1% (9/47) - functional urodynamics disorders (neurogenic dysfunction of the bladder). Patients were divided into groups depending on the stage of chronic kidney disease: the 1-st group included 30 patients with CKD stage 2 (GFR 60 to 90 ml/min/1.73m^2), the 2nd group - 17 patients with CKD stage 3 (GFR from 30 to 59 ml/min/1.73m^2). Among the 47 patients examined, 37 were treated with angiotensin-converting enzyme (ACE) inhibitors, i.e. 80.0% (24/30) of patients with CKD stage 2 and 76.5% (13/17) - with CKD stage 3.

The main clinical data and indices are presented in table 1.

There were no differences in age and gender among the groups under study. Patients in group 2 (CKD stage 3) had significantly lower height rates ($p = 0.024$), body weight ($p = 0.031$), hemoglobin ($p = 0.012$), and statistically higher levels compared to the control group children of systolic ($p = 0.025$) and diastolic blood pressure ($p = 0.026$), uric acid ($p = 0.019$) (table 1) compared with the control group. In patients with CKD in both groups, levels of CRP ($p = 0.038$ and $p = 0.009$, respectively) and microalbuminuria ($p = 0.001$ and $p = 0.0001$, respectively) were reliably higher than those in the control group.

The comparative characteristics of the echocardiographic examination results are presented in table 2. In children with CKD, during the disease progression, the left ventricular cavity is enlarged, which is confirmed by the reliable increase of ESI ($p = 0.011$) and EDI ($p = 0.016$) in patients with CKD stage 3 compared to that in the control group. The LVMI was reliably higher compared to that in the control group both in patients with CKD stage 2 ($p = 0.025$) and in those with CKD stage 3 ($p = 0.007$).

Table 1. Main clinical data and indices in the examined patients

Indices, units of measure	Groups of examined patients		
	Group 1 (n=30)	**Group 2 (n=17)**	**Control group (n=20)**
Gender, m/f	14/16	10/7	9/11
Age, years	11.28(6.46;16.72)	11.08(7.80;15.86)	10.78(6.98;16.16)
Height (Z-score)	-0.09(-1.05;0.70)	-0.88(-2.16;-0.33)^{c}	0.44(-0.16;1.24)$^{\#}$
Body weight (Z-score)	-0.95(-1.67;0.47)	-0.98(-1.59;0.01)^{c}	0.12(-0.27;0.72)$^{\#}$
BMI (Z-score)	0.27(-0.35;0.66)	-0.97(-1.71;0.35)	-0.04(-0.11;0.39)
Hemoglobin, g/l	122(113;129)	105(92;112)^{c}	125(119;130)$^{\#}$
Systolic BP, mm Hg	116(112;126)	122 (118;131)^{c}	114 (108;121)$^{\#}$
Diastolic BP, mm Hg	73(65;82)	83(77;87)^{c}	68(62;78)$^{\#}$
GFR, ml/min	72.0(66.7;82.0)$^{c\#}$	40.6(36.8;51.8)^{c}*	100.6(95.8;124.2)$^{*\#}$
Blood serum uric acid, mmol/l	0.33(0.27;0.39)	0.45(0.38;0.61)^{c}*	0.24(0.22;0.34)$^{\#}$
CRP, mg/ml	4.07 (3.27;7.11)$^{c\#}$	7.28 (6.99;11.08)^{c}*	1.03 (0.06;1.88)$^{a*\#}$
Microalbuminuria, mg/ml	19.6 (14.3;47.2)$^{c\#}$	84.2 (42.7;287.6)^{c*}	3.5 (2.7;15.1)$^{*\#}$

Note. *- - the probable difference when compared with the indicators of group 1; # - the probable difference when compared with the indicators of group 2; c – the probable difference when compared with the indicators of the control group; a –CRP level was determined in 17 children in the control group.

Table 2. Main morphological parameters of the left ventricle in the examined children, (Me (Q25; Q75))

Indices, units of measure	Groups of examined patients		
	Group 1 (n=30)	Group 2 (n=17)	Control group (n=20)
EDI, мл/м^2	57.9 (53.5; 66.2)	62.9(59,9; 71,6)^{c}	53.6(47.8; 60.0)#
ESI, мл/м^2	10.9(14.5; 22.6)	22.1(19.5; 26.3)^{c}	20.5(15.0; 23.2)#
EF, %	63.9(60.9; 69.2)	63.4(63.1; 69.2)	66.6(65.2; 73.7)
LVMI (г/м^{2,7})	31.7(28.0; 39.2)	34.2(30.7; 44.1)^{c}	30.8(26.2; 34.6)#*
LVMI (Z-score)	1.69(1.04; 2.67)^{c}	2.42(1.79; 3.09)^{c*}	0.37(-0.17; 1.07)$^{*\#}$
LVRWT	0.36(0.25; 0.51)	0.36(0.33; 0.39)	0.34(0.32; 0.41)
LVH (%)	36.70%	47.00%	-

Note. *- the probable difference when compared with the indicators of group 1; # - the probable difference when compared with the indicators of group 2; c – the probable difference when compared with the indicators of the control group.

Table 3. Dynamics of the brachial artery diameter during the endothelium dependent vasodilation test in the examined patients

Indices, units of measure	Groups of examined patients		
	Group 1 (n=30)	**Group 2 (n=17)**	**Control group (n=20)**
FMD, %	9.7 (6.3; 13.7)$^{c\#}$	5.9 (3.2; 8.9)*^{c}	17.6 (11.6; 25.2)*$^{\#}$
FMD ≤10%, % (n)	90.0 (27)	100.0 (17)	5.0 (1)

Note. *- the probable difference when compared with the indicators of group 1; # - the probable difference when compared with the indicators of group 2; c – the probable difference when compared with the indicators of the control group.

FMD index was reliably lower in patients of group 1 and 2 (H=42.7, p= 0.0000; p1-2=0.013; $p_{controls-1}$=0.033; $p_{controls-2}$=0.0000) compared to that in the control group (table 3). Endothelial dysfunction was detected in 90% of patients with CKD stage 2 and in 100% of those with CKD stage 3.

A significant negative correlation between levels of FMD and LVMI (r=-0.49, p=0.031), CRP (r=-0.76, p<0.001), microalbuminuria (r=-0.65, p<0.001) was found in all patients with CKD.

Table 4. Spearman's linear correlation analysis of endothelial function, inflammatory indexes and LVMI in the children with CKD

Indices	FMD	CRP	Microalbuminuria	LVMI
FMD	X			
CRP	-0.76*	X		
Microalbuminuria	-0.65*	0.37	X	
LVMI	-0.49*	0.29	0.36	X

Note. * - $p<0.05$

Discussion

In previous studies it has been determined that patients with CKD have endothelial dysfunction, which aggravates the risk of cardiovascular complications (Satoh 2012). Endothelial dysfunction along with inflammation, microalbuminuria plays an important role as a nonconventional risk factor for cardiovascular events in CKD. LVH is one of the major traditional risk factors for cardiovascular complications in the pediatric population of patients with CKD.

However, the mechanisms underlying the association between these factors are completely unclear, particularly in children with mild-to-moderate renal function decrease.

In the present study, it was found that children with CKD stages 2 or 3 had signs of systemic inflammation, endothelial dysfunction and left ventricular hypertrophy. This information is consistent with previous studies performed among adult patients (Yilmaz et al 2011). The results indicate that the levels of systemic inflammation (at CRP $H = 35.2$, $p = 0.001$) and endothelial dysfunction (at the level of FMD $H = 42.7$, $p = 0.0000$) grow with the renal function decreasing, that is, during the progression of CKD.

At present, fundamental studies confirm that inflammation can lead to the endothelial cells damage (Yilmaz et al 2011; D'Apolito et al 2015) and, conversely, that the endothelium synthesizes various inflammatory molecules (Carrero et al 2009). Recent data suggest that inflammation, oxidative stress and endothelial dysfunction in patients with CKD have a synergistical effect. The data of these studies are confirmed in our work by the presence of a strong correlation between levels of CRP and FMD.

Our study also demonstrated the link between endothelial dysfunction and left ventricular hypertrophy in pediatric patients with CKD and mild-to-moderate renal dysfunction. Despite the fact that LVH is common in patients with CKD, first of all, its development is associated with inflammation and oxidative stress. However, until now, the mechanisms underlying the development of LVH in pediatric CKD patients are still not clearly defined.

We assume that it can be endothelial dysfunction that plays a decisive role in the remodeling of the left ventricle in the cohort of patients we studied. In detail, the effect of endothelial dysfunction on the LVH development was studied on the hypertension model. It has been proven that endothelin, as a powerful microvascular constrictor and pro-inflammatory agent, is released from the damaged endothelium and promotes the development of heart hypertrophy. However, we can not extrapolate this mechanism to our study, because among children with CKD stages 2-3, a very small number of patients had hypertension, and besides, we have not obtained a reliable association with LVMI.

Elucidation of association between endothelial dysfunction and hypertension in hypersympathicotonia should be considered as a promising direction for further studies on the mechanisms of cardiovascular events in patients with CKD at the initial stages.

Conclusion

Children with chronic pyelonephritis have early signs of endothelial dysfunction and systemic inflammation, which worsens during mild-to-moderate CKD progression. The presence of the reliable correlations between endothelial dysfunction, systemic inflammation and LVMI suggests the involvement of the endothelium in the development and maintenance of chronic inflammation and the left ventricular hypertrophy formation.

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