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Determinants of heart and arterial system damage in children with chronic kidney disease

Czynniki ryzyka uszkodzenia serca i tętnic u dzieci z przewlekłą chorobą nerek

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Key words

chronic kidney disease, children, arteries, heart, calcium-phosphate disturbances

Słowa kluczowe

przewlekła choroba nerek, dzieci, tętnice, serce, zaburzenia gospodarki wapniowo-fosforanowej

Summary

Introduction. Children with chronic kidney disease (CKD) are among pediatric patients with highest cardiovascular risk.

Aim. The aim of the study was to evaluate heart and arterial system in children with CKD in relation to selected clinical and biochemical parameters and to assess usefulness of NT-proBNP as a marker of cardiovascular damage in this group of patients.

Material and methods. In 17 children (13.5 ± 4.3 years), with CKD stage 2-5, we assessed: echocardiography, carotid intima-media thickness (cIMT), pulse wave velocity (PWV) and analysis, N-terminal prohormone B-type natriuretic peptide (NT-proBNP), blood pressure, medications, and selected biochemical parameters.

Results. Left ventricular mass index (LVMI) was 29.3 ± 6.2 g/m^{2,7}, cIMT 0.46 ± 0.05 mm, PWV 4.65 ± 0.94 m/s, augmentation index at heart rate 75/min (AI x 75HR) 5.85 ± 16.32%, aortic systolic blood pressure (AoSP) 102.0 ± 12.8 mmHg, and aortic diastolic blood pressure (AoDP) 73.9 ± 13.0 mmHg. LVMI correlated with NT-proBNP (r = 0.55, p = 0.029), PTH (r = 0.69, p = 0.003), alkaline phosphatase (ALP) (r = 0.65, p = 0.009); PWV with cIMT (r = 0.66, p = 0.004), left ventricular posterior wall thickness (r = 0.56; p = 0.025); PWV/height ratio with GFR (r = -0.52, p = 0.032), subendocardial viability ratio (r = -0.52, p = 0.034); AI x 75HR with NT-proBNP and ALP (r = 0,58, p = 0.015; r = 0.57, p = 0.02); AoSP and AoDP with NT-proBNP (r = 0.63, p = 0.006; r = 0.50, p = 0.04) and PTH (r = 0.62, p = 0.007; r = 0.57, p = 0.02). We found tendency toward correlations of calcium carbonate dose with PWV (r = 0.45, r = 0.08) and cIMT (0.49, p = 0.055).

Conclusions. 1. In children with CKD, NT-proBNP is a useful marker of left ventricular hypertrophy, arterial stiffness and central blood pressure. 2. In pediatric patients with CKD calcium-phosphate disturbances seem to be key determinants of left ventricle mass and arterial stiffness. 3. Calcium carbonate dose may influence arterial stiffness and IMT in children with CKD, but this relation requires further investigations in larger groups of patients.

Streszczenie

Wstęp. Dzieci z przewlekłą chorobą nerek (PChN) cechują się najwyższym ryzykiem sercowo-naczyniowym wśród pacjentów pediatrycznych.

Cel pracy. Celem pracy była ocena serca i tętnic u dzieci z PChN w powiązaniu z wybranymi parametrami klinicznymi i biochemicznymi oraz określenie przydatności oznaczania NT-proBNP jako markera uszkodzenia układu sercowo-naczyniowego w tej grupie chorych.

Materiał i metody. U 17 dzieci w śr. wieku 13,5 ± 4,3 lat z PChN st. 2-5 oceniono: badanie echokardiograficzne, kompleks błona środkowa-wewnętrzna t. szyjnych wspólnych (cIMT), kształt i prędkość fali tętna (PWV), NT-proBNP, ciśnienie tętnicze, leki i wybrane parametry biochemiczne.

Wyniki. W badanej grupie śr. indeks masy lewej komory (LVMI) wynosił 29,3 ± 6,2 g/m^{2,7}, cIMT 0,46 ± 0,05 mm, PWV 4,65 ± 0,94 m/s, wskaźnik wzmocnienia skorygowany do akcji serca 75/min (AIx75HR) 5,85 ± 16,32%, aortalne ciśnienie skurczowe (AoSP) 102,0 ± 12,8 mmHg, rozkurczowe (AoDP) 73,9 ± 13,0 mmHg. Wartość LVMI korelowała z NT-proBNP (r = 0,55, p = 0,029), PTH (r = 0,69, p = 0,003), fosfatazą alkaliczną

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(r = 0,65, p = 0,009); PWV z cIMT (r = 0,66, p = 0,004) i grubością tylnej ściany lewej komory (r = 0,56; p = 0,025); wskaźnik PWV/wzrost z GFR (r = -0,52, p = 0,032) i wskaźnikiem wypełnienia t. wieńcowych (r = -0,52, p = 0,034); AIx75HR z NT-proBNP i fosfatazą alkaliczną (r = 0,58, p = 0,015; r = 0,57, p = 0,02); AoSP i AoDP z NT-proBNP (r = 0,63, p = 0,006; r = 0,50, p = 0,04) i PTH (r = 0,62, p = 0,007; r = 0,57, p = 0,02). Wykazano tendencję do korelacji dobowej dawki węglanu wapnia z PWV (r = 0,45, r = 0,08) i cIMT (0,49; p = 0,055).

Wnioski. 1. U dzieci z PChN NT-proBNP jest użytecznym markerem przerostu lewej komory serca, sztywności tętnic i ciśnienia centralnego. 2. U pediatrycznych pacjentów z PChN zaburzenia gospodarki wapniowo-fosforanowej wydają się być kluczową determinantą masy lewej komory i sztywności tętnic. 3. Dawka węglanu wapnia może wpływać na sztywność tętnic i grubość kompleksu IMT u dzieci z PChN, ale ta zależność wymaga dalszych badań na większych grupach pacjentów.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of increased mortality in children and young adults with chronic kidney disease (CKD). The risk of cardiovascular death in patients aged 25-34 years, with CKD stage 5, is the same as in general population at the age of 75 (1). Patients with CKD present with both: typical cardiovascular risk factors (e.g. hyperlipidemia, hypertension, insulin resistance), which occur more frequently in course of CKD (2), and non-typical, uremia-related cardiovascular risk factors (e.g. anemia, hypervolemia, chronic inflammation, calcium-phosphate metabolism disturbances) which are particularly important in CVD development in young adults (3-5). Cardiovascular complications of CKD include structural and functional damage to the heart and abnormalities within the blood vessels (6).

Within the heart, CKD leads to left ventricular hypertrophy (LVH) and diastolic dysfunction. LVH in children can be assessed on echocardiography by calculating left ventricular mass index (LVMI). LVH is a frequent finding in children with CKD (7-9). Diastolic dysfunction can also be determined on echocardiography, as a decrease in early/atrial ventricular filling velocity ratio (E/A ratio) and tissue Doppler imaging (TDI) abnormalities. Disturbed diastolic function, correlating with decreasing GFR, has been reported in children with CKD (10, 11).

In response to cardiac structural damage, myocardium cells excrete B-type natriuretic peptide (BNP) and its inactive metabolite – N-terminal prohormone BNP (NT-proBNP). The latter is a useful biochamical marker of cardiac strain in both adults and children (12, 13).

Within the blood vessels, both atherosclerosis and arterial calcifications develop in course of CKD. Augmentation index, aortic pulse wave velocity and carotid intima media thickness are well established surrogate markers of vascular damage and cardiovascular risk in adults with CKD, but they still need standardization and validation in pediatric population (14, 15).

AIM

The aim of this study was to evaluate the heart and arterial system in children with CKD in relation to selected clinical and biochemical parameters and to assess usefulness of NT-proBNP as a marker of cardiovascular damage in this group of patients.

MATERIAL AND METHODS

We studied 17 children (11 boys and 6 girls) aged from 5.4 to 17.1 years (mean 13.5 ± 4.3 years) treated in the Department of Pediatrics and Nephrology of Medical University of Warsaw for chronic kidney disease. Causes of CKD in the analyzed children were as follows: congenital anomalies of kidney and urinary tract (CAKUT) in 9 (52.9%), glomerulonephritis in 4 (23.5%), other causes in 3 (17.6%): cortical necrosis after post-ischemic acute kidney injury in 2, lupus nephritis in 1; in 1 (5.9%) child cause of CKD was unknown. Children with congenital heart defects were excluded from the study.

In all studied children cardiovascular status was evaluated by assessment of peripheral blood pressure, 2d echocardiography, assessment of arterial stiffness by applanation tonometry and carotid intima media thickness by 2d ultrasonography, and assessment of serum NT-proBNP level.

Peripheral blood pressure [mmHg] was measured oscillometrically in each patient on the right arm using the Welch Allyn ASM 300 Patient Monitor device (Welch Allyn, USA).

Detailed conventional 2-dimensional echocardiographic examinations (Philips iE33 xMATRIX Echocardiography System, Philips Healthcare, Netherlands) were performed in all patients by the same experienced paediatric cardiologist following the same protocol. Left ventricular end systolic (LVES) and end diastolic diameters (LVED), interventricular septum and posterior wall thicknesses in systole and in diastole (IVES, IVED, PWES, PVED, respectively) were measured. LVM was calculated using the Devereux formula (16), and LVM index (LVMI; mass divided by height raised to a power of 2.7 $g/m^{2,7}$) was used to evaluate LVH (17). LVH was defined as LVMI greater than the 95th percentile for normal children and adolescents (18). All parameters were measured during three consecutive cardiac cycles, and their mean value was calculated.

Arterial pulse waveform and aortal pulse wave velocity were evaluated using the Sphygmocor device (AtCor Medical, Australia). Peripheral pressure waveforms were recorded from the radial artery at the right wrist, using applanation tonometry. After 20 sequential waveforms had been acquired, a validated generalized

transfer function was used to generate the corresponding central aortic pressure waveform. We evaluated the following parameters: aortic systolic pressure (AoSP) [mmHg], aortic diastolic pressure (AoDP) (mmHg], aortic pulse pressure (AoPP) [mmHg], augmentation pressure (AP) [mm Hg], augmentation index (AIx(AP/PP), (AIx(P2/P1)) [%], augmentation index (AIx(AP/PP)) corrected for heart rate of 75 beats per minute (AIx75HR) [%], and an index of myocardial oxygen supply and demand, subendocardial viability ratio (SEVR or Buckberg index) [%]. AP was calculated as the difference between the second (P2) and first (P1) systolic peak of the central pressure waveform. AIx was defined as the AP divided by pulse pressure and expressed as a percentage. Because AIx is influenced by heart rate, an index normalized for heart rate of 75 bpm (AIx-75HR) was used. SEVR was defined as the ratio of diastolic and systolic area under the curve (19-21). Only high-quality recordings, defined as an in-device quality index > 80%, were included in the analysis. PWV was calculated as the difference in the carotid-to-femoral path length divided by the difference in the R wave from the ECG to the foot of the pressure wave taken from the superimposed ECG and pressure tracings. The distance traveled by the flow wave was measured with an external tape measure over the body surface, as the distance from the right carotid sampling site to the manubrium subtracted from the distance from the manubrium to the right femoral sampling site. All pulse wave analyses and velocity measurements were performed in the sitting position in a quiet, temperature-controlled room (20 ± 5°C) after a period of rest (for at least 5 minutes).

Carotid intima media thickness (cIMT) was measured in the patient group by the same ultrasonographer following the same protocol using Aloka Prosound Alpha6 (Hitachi Aloka Medical Ltd., Japan) ultrasound system and a 13-MHz linear transducer. Intima-media thickness was defined as the mean distance from the leading edge of the lumen-intima interface to the leading edge of the media adventitia interface of the far wall, approximately 1 cm proximal to the carotid bulb. Six determinations of IMT (three on the left, and three on the right side) were obtained and averaged (15).

NT-proBNP concentration [pg/mL] was determined using Enzyme-Linked Fluorecent Assay (ELFA) technique. Normal value for NT-proBNP was < 125.0 pg/mL (VIDAS, BioMerieux, Lyon, France). In all children following biochemical parameters were assessed: hemoglobin [g/dL], serum creatinine [mg/dL], urea [mg/dL], uric acid [mg/dL], glucose [mg/dL], albumin [g/dL], calcium [mEq/l], phosphate [mEq/l], calcium-phosphate product [mEq^2/l^2], parathormone [pg/mL], alkaline phosphatase [U/L], 25(OH) vitamin D [ng/mL], total, HDL (high-density lipoprotein), LDL (low-density lipoprotein) cholesterol [mg/dL], triglycerides [mg/dL], acid-base balance parameters: pH, HCO3- [mEq/L], BE (base excess) [mEq/L]. Intact parathormone was assessed using IMMULITE 2000 assay (Siemens Healthcare Diagnostics, Deerfield, IL, USA), 25(OH)D using ARCHIECT assay (Abbott Laboratories, Abbott Park, IL, USA); other biochemical parameters were assessed with standard laboratory methods on VITROS 250 analyzer (Ortho Clinical Diagnostics, Rochester, NY, USA). Glomerular filtration rate was calculated using revised Schwartz formula (22). Target levels of calcium, phosphate and PTH were taken after National Kidney Foundation K/DOQI guidelines for children published in 2005 (23), target 25(OH)D levels after Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe (24).

In our clinical analysis, we also included data on the presence of hypertension and medications used (antihypertensives, sodium bicarbonate, calcium carbonate, iron, erithropoiesis stimulating agents).

Statistical analyses were performed using the Statistica 9.0 PL software (StatSoft, College Station, TX, USA). Normal variable distribution was tested using the Shapiro-Wilk test. Normally distributed variables are presented as mean values ± standard deviation, and non-normally distributed variables as medians and ranges. Differences in normally distributed variables were tested using the Student t test, and differences in non-normally distributed variables were tested using the Mann-Whitney U test. Correlations between variables were evaluated using Pearson and Spearman correlations, where applicable. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of the patients with chronic kidney disease are shown in table 1. Among 17 analyzed children, congenital anomalies of the kidney and urinary tract were the most common cause of CKD. Most children were in stage 3 of CKD. Among 4 children with end-stage renal disease (ESRD), 3 were treated with automated peritoneal dialysis and 1 with intermittent hemodialysis. Eleven (64.7%) children had diagnosed arterial hypertension and angiotensin-converting enzyme inhibitors (ACEi) were most frequently used antihypertensive medications. Nine (52.9%) patients were treated with calcium carbonate, 5 among these 9 children with alphacalcidol, and 5 (29.4%) with erythropoeisis stimulating agents.

Biochemical parameters in the study group are presented in table 2. In the study group hemoglobin below recommended level was found in 4 (23.5%) patients. Fasting glucose level was normal in all patients apart from two children: one boy with CKD stage 3 in the course of posterior urethral valves and one girl with CKD stage 5 treated with automated peritoneal dialysis. Serum albumin level was also normal in all but one child (3.4 g/dL) with CKD stage 5 in the course of membranoproliferative glomerulonephritis with preserved residual renal function and substantial proteinuria. In all children serum calcium and phosphate level were within recommended target range, and PTH

level was below target level in 6 (35.3%) patients; vitamin D deficiency (25(OH)D < 20 ng/mL) was recognized in 6 (35.3%), and suboptimal status (25(OH)D: 20-30 ng/mL) also in 6 (35.3%) children.

Table 1. Clinical characteristics of children with chronic kidney disease.

Number of patients (n)	17
Sex (boys/girls)	11/6 (64.7%/35.3%)
Age [years]	13.5 ± 4.3 (5.4-17.1)
Causes of CKD (n, %) CAKUT GLOMERULONEPHRITIS OTHER UNKNOWN	 9 (52.9%) 4 (23.5%) 3 (17.6%) 1 (5.9%)
CKD stage (n, %) 2 3 4 5	 5 (29.4%) 7 (41.2%) 1 (5.9%) 4 (23.5%)
Arterial hypertension (n, %)	11 (64.7%)
Antihypertensive medications (n, %) ACEi ARB Calcium channel antagonists Beta-adrenolytics	 9 (52.9%) 2 (11.8%) 7 (41.2%) 2 (11.8%)
Calcium carbonate [g/24 h]	1.0 (0.0-8.0)
Alphacalcidol [μg/week]	0.0 (0.0-2.0)
ESA (n, %)	5 (29.4%)

CKD – chronic kidney disease, CAKUT – congenital anomalies of kidney and urinary tract, ACEi – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, ESA – erythropoiesis-stimulating agent

Table 2. Biochemical parameters in children with chronic kidney disease.

Urea [mg/dL]	60.53 ± 32.25
Creatinine [mg/dL]	1.3 (0.7-10.3)
GFR ac. to Schwartz [mL/min/1.73 m^2]	41.3 ± 25.2
Hemoglobin [g/dL]	12.4 ± 1.6
Glucose [mg/dL]	90.7 ± 16.78
Albumin [g/dL]	4.32 ± 0.32
Calcium [mEq/l]	5.00 ± 0.23
Phosphorus [mEq/l]	2.83 ± 0.55
Calcium x Phosphorus [mEq^2/l^2]	14.12 ± 2.79
PTH [pg/mL]	46.3 (10.9-721)
ALP (U/L]	173.5 (61-401)
25(OH)D [ng/mL]	22.9 (11.3-53.6)
Triglycerides [mg/dL]	112.8 ± 66.5
Total cholesterol [mg/dL]	196.0 ± 58.0
HDL cholesterol [mg/dL]	61.8 ± 15.2
LDL cholesterol [mg/dL]	112.4 ± 51.5
Uric acid [mg/dL]	6.62 ± 1.48
pH	7.41 ± 0.03
HCO3-[mEq/L]	25.13 ± 1.89
BE [mEq/L]	0.7 (-3.1-5.7)

GFR – glomerular filtration rate, PTH – parathormone, ALP – alkaline phosphatase, 25(OH)D – 25-hydroxyvitamin D, HDL – high-density lipoprotein, LDL – low-density lipoprotein, BE – base excess

Markers of cardiovascular damage are presented in table 3. Left ventricular hypertrophy was found in 2 (11.8%) children, both with ESRD: one boy with membranoproliferative GN treated with HD, and one girl with unknown cause of CKD treated with APD. Left ventricle mass did not differ significantly between children with arterial hypertension and normal blood pressure, also no significant differences in left ventricle mass between children with different stages of CKD were found. NT-proBNP was elevated in 5 children: 1 with CKD stage 2, 1 with CKD stage 3, and 3 with CKD stage 5. The boy with elevated NT-proBNP (933 pg/mL) and CKD stage 2 had arterial hypertension requiring two antihypertensive medications (enalapril, metoprolol). Two children with LVH were characterized by substantially highest NT-proBNP levels (1579 and 28382 pg/mL, respectively).

Table 3. Markers of arterial and heart damage in the study group.

SBP [mmHg]	118.2 ± 13.1
DBP [mmHg]	72.2 ± 13.0
LVMI [g/m$^{2.7}$]	29.3 ± 6.2
cIMT [mm]	0.46 ± 0.05
PWV [m/s]	4.7 ± 0.9
AoSBP [mmHg]	102.0 ± 12.8
AoDBP [mmHg]	73.9 ± 13.0
AoPP [mmHg]	28.0 ± 4.3
AP [mmHg]	1.3 (-4.7-15)
AIx (AP/PP) [%]	6.3 (-18-44)
AIx (P2/P1) [%]	107 (19.7-178)
AIx75HR [%]	10.1 ± 18.7
SEVR [%]	155.3 ± 23.5
NT-proBNP [pg/mL]	74 (19-28382)

SBP – systolic blood pressure, DBP – diastolic blood pressure, LVMI – left ventricular mass index, cIMT – carotid intima-media thickness, PWV – pulse wave velocity, AoSBP – aortic systolic blood pressure, AoDBP – aortic diastolic blood pressure, AoPP – aortic pulse pressure, AP – augmentation pressure, AIx – augmentation index, P1 – first systolic peak of the central pressure waveform, P2 – second systolic peak of the central pressure waveform, SEVR – subendocardial viability ratio, NT-proBNP – N-terminal prohormone B-type natriuretic hormone

In the study group LVMI correlated positively with NT-proBNP (r = 0.55, p = 0.029), PTH (r = 0.69, p = 0.003), and alkaline phosphatase (r = 0.65, p = 0.009); PWV with cIMT (r = 0.66, p = 0.004) and left ventricular posterior wall thickness (r = 0.56; p = 0.025); PWV/height ratio negatively with GFR (r = -0.52, p = 0.032) and with subendocardial viability ratio (Buckberg index) (r = -0.52, p = 0.034); AIx (P2/P1) with NT-proBNP, phosphate, calcium-phosphate product, and alkaline phosphate (r = 0,58, p = 0.015; r = 0.48, p = 0.05; r = 0.52, p = 0.03; r = 0.57, p = 0.021); AI x 75HR positively with NT-proBNP and alkaline phosphatase (r = 0,58, p = 0.015; r = 0.57, p = 0.02); AoSP and AoDP with NT-proBNP (r = 0.63, p = 0.006; r = 0.50, p = 0.04) and PTH (r = 0.62, p = 0.007; r = 0.57, p = 0.02). Additionally, we found

tendency toward positive correlations of daily calcium carbonate dose with PWV (r = 0.45, r = 0.08) and cIMT (0.49, p = 0.055).

DISCUSSION

Evidence from epidemiological and clinical studies as well as in vitro data have shown that CVD begins early in the course of renal failure and progresses rapidly on dialysis (14). Traditional risk assessment approaches, such as the Framingham risk score, are not designed to cope with the specific combination of risk factors in CKD patients and underestimate the cardiovascular threat in this population. Thus early, non-invasive markers of subclinical heart and vessel damage are commonly used in this group of patients, also in children. In this study we tried to recognize risk factors for subclinical heart and arterial wall damage in children with CKD stage 2-5.

Assessment of arterial stiffness is a measure of cumulative vascular pathology and can be evaluated by both calculation of augmentation indices and central aortic pulse wave velocity. Pulse waveform is the sum of a wave generated by contraction of the left ventricle and propagating away from the heart within the arterial tree, and a reflected wave returning from the peripheral vessels (25). With increased arterial stiffness, pulse wave velocity is large and the return of reflected wave coincides with the systolic phase of primary pulse wave, resulting in augmentation of late systolic aortic pressure (26). The size of this augmentation of the central aortic pressure and central pulse wave velocity were found to be an independent cardiovascular risk factor in adult patients with renal failure (27-29). In our small group of children with CKD, arterial stiffness was positively related to alkaline phosphatase, phosphate level and calcium-phosphate product, as well as daily calcium carbonate dose. Our results are in agreement with other pediatric studies, in which PWV increased in association with elevated phosphate, calcium-phosphate product, decreased Fetuin-A level, and cumulative dose of calcitriol (30-33). These results suggest that calcium phosphate disturbances, along with calcium overload can lead to calcium deposition in vascular wall, thus impairing its elastic properties in children with CKD.

As growth contributes to the physiological properties of the arterial tree, in particular arterial elasticity, PWV is commonly normalized for height in pediatric population. Negative correlation of PWV/height with GFR clearly shows exacerbation of vascular damage with progression of CKD. Interestingly, PWV/height ratio correlated negatively with subendocardial viability ratio, which is marker of myocardial perfusion, suggesting that arterial stiffness increases substantially the heart muscle burden and impairs coronary blood flow already in children.

Carotid intima-media thickness (cIMT) is a validated morphological parameter reflecting structural changes in large elastic arteries and increased cIMT is considered to be an early stage in atherosclerotic plaque formation. In our study group cIMT correlated positively with PWV and calcium carbonate dose, the latter being consistent with the study by Litwin et al (34). In adult patients with end-stage renal disease (ESRD) increased cIMT has been found to predict coronary events and mortality (35). Increased cIMT has also been revealed in both pediatric CKD patients in stages 2-4 (36) and in patients on dialysis (33). Pediatric studies have shown that cIMT correlated with a higher vitamin D dosage (33, 36, 37), and with both low and very high levels of 1,25-dihydroxyvitamin D (37). Thus, ours and other authors' results suggest that mineral disturbances can accelerate formation of atherosclerotic plaque in pediatric CKD patients.

Pulse wave analysis in the radial artery allows estimation of central aortic blood pressure and pulse pressure. In adults, central aortic pressure was found to be a better predictor of cardiovascular risk compared to peripheral arterial pressure (38-40). Results of the Chronic Renal Insufficiency Cohort (CRIC) study in 2351 adult patients with CKD suggest that elevated central aortic pulse pressure is a risk factor for presence of carotid plaque (41). We have found that central systolic and diastolic blood pressure were related to PTH level. Thus, we may hypothesize that mineral metabolism disorders in CKD not only influence vessel wall but also increase aortic blood pressure, which may pose additional cardiovascular risk factor in this group of patients.

The impact of vitamin D on vascular calcification was studied in both experimental and clinical studies. Both 25(OH)D and 1,25(OH)2D can have a direct effect on vascular smooth muscle cells (VSMC) by induction of calcium uptake, decreasing cell proliferation and induction of VSMC conversion into osteoblasts (42). Studies in pediatric CKD patients revealed that high doses of vitamin D increase cIMT and vascular calcification (36, 37). On the other hand, adult patients with ESRD treated with vitamin D are characterized by significantly higher survival rate compared to those without vitamin D formulation (43, 44). Probably, there is a narrow therapeutic window for vitamin D level protective for vascular health. In our study group we have not found any significant correlations between markers of vascular or heart damage and 25(OH)D level or alphacalcidol level, which may be a consequence of small study group. On the other hand, we have not evaluated 1,25(OH)2D levels and only 5 out of 17 children obtained alphacalcidol which could have weaken our analysis.

In CKD patients both increase in preload (fluid retention, anemia) and afterload (hypertension, increased aortic stiffness) is present. As a compensatory mechanism, the left ventricle increases its output, but this leads to a progressive hypertrophy and cardiac systolic and/or diastolic dysfunction (45). In our study group left ventricular hypertrophy (LVMI > 38.6 g/m^{2,7}) was found in only 2 (11.8%) children, both with ESRD.

In other studies prevalence of LVMI in pediatric CKD population varied from 20-30% in predialysis stages up to 85% in ESRD patients (45, 46). Relatively low prevalence of LVH in our group may be again consequence of small patient sample. Similarly to markers of vascular damage, we have found positive correlations between left ventricular mass and PTH and alkaline phosphatase, which, once again, suggest that calcium-phosphate disturbances substantially increase cardiovascular burden in this group of patients. We have not found any significant correlation between peripheral and central blood pressure and left ventricular mass, the latter being consistent with the results of study by Mencarelli et al (46). One may hypothesize that ambulatory blood pressure monitoring results instead of office blood pressure measurements could be more accurate in prognosing left ventricular mass in our group of patients.

B-type natriuretic peptide (BNP) was first identified in porcine brain in 1988 and originally was termed brain natriuretic peptide. Subsequently, it was detected that ventricular myocardium was the major source of circulating BNP. The main stimulus for increased BNP synthesis and secretion is wall stress. BNP is synthesized as a proBNP comprising 108 amino acids. In the circulation it is cleaved into the biologically active 32 amino-acid BNP and the biologically inactive 76 amino acid N-terminal fragment (NT-proBNP). BNP relaxes vascular smooth muscle, dilates arteries and veins, lowers blood pressure, and inhibits sympathetic activity and the rennin-angiotensin-aldosterone system. In kidneys BNP increases glomerular filtration and inhibits sodium reabsorption, thus promoting natriuresis and diuresis (47-49). BNP and NT-proBNP are mostly used as diagnostic biomarkers of acute heart failure (HF). According to American National Academy of Clinical Biochemistry (NACB) the use of BNP or NT-proBNP testing to rule out or to confirm the diagnosis of heart failure was assigned a class I, level of evidence A (50).

In our study group we have found positive correlations between NT-proBNP level and left ventricular mass, arterial stiffness and central blood pressure. Our results strongly suggest that measurement of serum NT-proBNP level can be a relatively cheap and easily accessible marker of cardiovascular burden in children with CKD. Nevertheless, studies evaluating usefulness of NT-proBNP in CKD patients have given so far inconsistent results. Caliskan Y et al. have not found any significant correlations between cIMT, PWV, AIx, and NT-proBNP in pediatric patients undergoing chronic peritoneal dialysis (51). On the other hand, Rinat et al. have found, similarly to our results, positive correlation between LVMI, systolic and diastolic blood pressure vs. NT-proBNP in 75 children with CKD stage 3-5 (13). Also analysis of adult CKD patients from CRIC cohort have shown that NT-proBNP is a very useful marker of left ventricular hypertrophy (12). Moreover, Gromadziński et al. proved that in adults with CKD left ventricular diastolic dysfunction was associated with significantly higher NT-proBNP levels (52).

In summary, our results suggest that in children with chronic kidney disease NT-proBNP is a useful, non-invasive, easily-accessible serum marker of left ventricular hypertrophy, arterial stiffness and central blood pressure. Numerous significant dependences let us draw the conclusion that calcium-phosphate disturbances seem to be key determinants of left ventricle mass and arterial stiffness in these group of patients. We also think that calcium carbonate dose may influence arterial stiffness and intima-media thickness in children with CKD, but this relation certainly requires further investigations in larger groups of patients.

CONCLUSIONS

1. In children with CKD NT-proBNP is a useful marker of left ventricular hypertrophy, arterial stiffness and central blood pressure.
2. In pediatric patients with CKD calcium-phosphate disturbances seem to be key determinants of left ventricle mass and arterial stiffness.
3. Calcium carbonate dose may influence arterial stiffness and IMT in children with CKD, but this relation requires further investigations in larger groups of patients.

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