AMINOTHIOLS IN HOMOCYSTEINE METABOLIC CYCLE ARE ASSOCIATED WITH CARDIOVASCULAR OUTCOMES IN CHILDREN WITH CHRONIC KIDNEY DISEASE

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OBJECTIVES

1. Less attention has been paid to evaluate subclinical cardiovascular disease (CVD) in early stage of pediatric chronic kidney disease (CKD).
2. Ambulatory blood pressure monitoring (ABPM) and arterial stiffness are the earliest detectable assessments of subclinical CVD.
3. Asymmetric dimethylarginine (ADMA) is an analog of L-arginine (ARG) to inhibit nitric oxide (NO) production; thus ARG-to-ADMA ratio (AAR) represents an NO index. Homocysteine (HCY) is a risk factor for CVD and it can be metabolized to L-cysteine (CYS). Given that HCY and ADMA/NO are closely linked and related to hypertension, we investigated whether ARG and HCY metabolites, arterial stiffness, ABPM profile, and left ventricular hypertrophy are inter-related to each other in children and adolescents with early CKD.

Table 1. Anthropometric, biomedical, and cardiovascular characteristics in children and adolescents with chronic kidney disease (CKD) stages 1–3Weights and functional parameters

CKD stage	1	2–3
	N = 34	N = 23
Gender: M: F	21:13	13:10
Underlying disease: CAKUT: non-CAKUT	25: 9	15: 8
Age, years	8.5 (6.1–13.9)	14.7 (9.6–16.8)*
Body height, cm	135 (116–160)	153 (137–111)
Body weight, kg	31.2 (21.5–51.8)	50.6 (27.5–57)
Body mass index, kg·m^{-2}	17.9 (15.8–21.2)	19.7 (15.5–22.7)
Overweight/obesity	9	5
Systolic blood pressure	112 (100–122)	112 (103–122)
Diastolic blood pressure	74 (67–81)	76 (68–80)
Hypertension (by office BP)	7	6
Blood urea nitrogen, mg/dL	12 (10–14)	17 (13–39)*
Creatinine, mg/dL	0.51 (0.44–0.59)	0.92 (0.76–1.27)*
eGFR, mL·min^{-1}·1.73 m^{-2}	109 (103–134)	64 (56–79)*
Urine total protein-to-creatinine ratio, mg/g	84 (61–368)	121 (49–668)
Hemoglobin, g/dL	13.9 (13.1–14.8)	13.7 (12.3–15)
Total cholesterol, mg/dL	165 (142–209)	156 (140–200)
LDL, mg/dL	87 (71–106)	91 (78–119)
Triglyceride, mg/dL	68 (45–112)	82 (54–100)
Glucose, mg/dL	89 (83–92)	87 (83–91)
Uric acid, mg/dL	5 (4.6–6.7)	7.9 (6.3–9)*
Hyperuricemia	10	17*
Sodium, mEq/L	141 (140–143)	141 (140–142)
Potassium, mEq/L	4.4 (4.2–4.5)	4.4 (4.1–4.7)
Calcium, mg/dL	9.6 (9.3–9.8)	9.5 (9–9.8)
Phosphate, mg/dL	4.7 (4.4–5.3)	4.2 (3.8–5)
LV mass, g	77.9 (51.2–112)	107 (56.3–143)
LVMI, g·m^{-2}	32.5 (25.8–40.1)	31.7 (25.7–45)
Left ventricular hypertrophy	6	7
cIMT, mm	0.38 (0.31–0.42)	0.35 (0.31–0.38)
PWV, m/s	3.88 (3.39–4.36)	3.75 (3.6–4.05)
AI, %	15.4 (11.7–21.6)	17.3 (10.6–28.5)
AASI	0.37 (0.26–0.43)	0.39 (0.27–0.5)

*P < 0.05 by the Mann-Whitney U-test.

Table 2. Blood pressure in children with chronic kidney disease (CKD) stages 1–3

CKD stage	1	2–3
	N = 25	N = 18
Hypertension (by office BP)	6 (24%)	4 (22%)
Abnormal ABPM profile, number of cases	18 (72%)	12 (67%)
Average 24-h BP > 95th percentile	7	6
Average daytime BP > 95th percentile	6	6
Average nighttime > 95th percentile	9	8
BP load ≥ 25%	15	11
Nocturnal decrease of BP < 10%	8	7

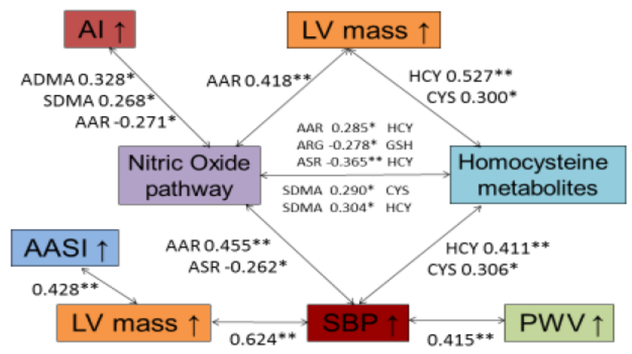

Figure 1. Schematic diagram showing inter-relationships among ARG metabolites in NO pathway, HCY metabolites, systolic BP, LV mass, and arterial stiffness (PWV, AI, and AASI). Double-headed arrows indicate significant association. *P < 0.05. **P < 0.01.

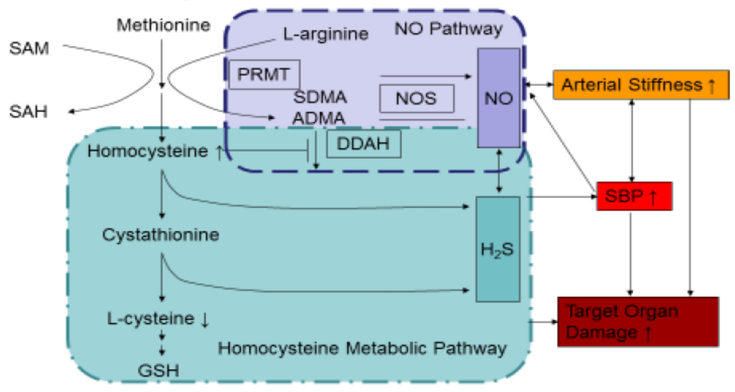

Figure 2. NO pathway and homocysteine metabolic pathway are closely linked but differently related to arterial stiffness, systolic BP, and hypertensive target organ damage in CKD.

Table 3. Plasma levels of CIT, ARG, ADMA, SDMA, and DMA and their combined ratios in children with CKD.

	CKD stage 1	CKD stage 2-3	Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)
	N=34	N=23		
ARG	107.7 (94.6–152.2)	116.6 (101.5–133.7)	1.00 (0.99–1.01)	1.07 (0.99–1.14)
ADMA	0.8 (0.5–1.6)	0.6 (0.4–1.2)	0.66 (0.28–1.54)	0.22 (0.01–8.18)
SDMA	0.8 (0.5–0.9)	1.1 (0.6–1.3)	1.56 (0.66–3.67)	1.64 (0.04–67.2)
HCY	6.3 (5.3–7.7)	9 (6.3–11.6)	1.23 (1.03–1.48)*	2.20 (1.36–3.53)*
CYS	180.7 (154.1–200.8)	169.8 (142–197.7)	1.00 (0.99–1.01)	0.96 (0.93–0.99)*
GSH	3.6 (2.7–5.1)	4.5 (3.3–5.8)	1.11 (0.85–1.44)	0.81 (0.42–1.56)
ARG-to-ADMA ratio	147.7 (80.3–231.1)	175.4 (113.2–251.5)	1.00 (1.00–1.00)	0.99 (0.98–1.00)
ADMA-to-SDMA ratio	1.25 (0.66–1.61)	1.17 (0.44–1.33)	0.52 (0.22–1.24)	2.69 (0.11–66.3)

*P < 0.05 by the Mann-Whitney U test. Adjusted odds ratio, each OR of the variable was adjusted by the other factors listed in the table in the logistic regression model

METHODS

1. This cross-sectional study included 57 pediatric patients with CKD stages 1-3.
2. The 24-hr ABPM data was collected for subjects aged 6 to 18 years using an Oscar II monitoring device (SunTech).
3. The levels of ARG, ADMA, symmetric dimethyarginine (SDMA, an isomer of ADMA), HCY, CYS, and GSH in the plasma were measured using HPLC (HP series 1100, Agilent Tec., Inc.)
4. The measurement of carotid intima-media thickness (cIMT) was assessed by the ProSound α7 ultrasound (Aloka).
5. Arterial stiffness parameters, PWV and AI, were determined by echo-tracking methods (e-TRACKING system; Aloka).

RESULTS

1. Children with CKD stages 2-3 were older, and had higher BUN, Cr, and uric acid but lower eGFR compared to those with CKD stage 1 (Table 1).
2. 20.9% (10/43) of patients were diagnosed as hypertension by office BP. Yet we found up to 69.8% (30/43) of children and adolescents with CKD stages 1-3 had abnormal ABPM (Table 2).
3. Children with CKD stages 2-3 had higher HCY, but lower CYS, compared to those with CKD stage 1 (Table 3).
4. Systolic BP was positively correlated with biomarkers AAR, HCY, and CYS, while negatively with ASR. Next, LV mass was positively correlated with AAR, HCY, and CYS (Figure 1).
5. Figure 2 represents a simplified schematic that summarizes our results into a potential pathological framework linking biomarkers, arterial stiffness, hypertension, and target organ damage.

CONCLUSIONS

1. BP abnormalities are highly prevalent in children and adolescents with early CKD, even in CKD stage 1.
2. BP abnormalities are correlated to AAR, HCY, and CYS, suggesting the role of NO and HCY pathway on CKD-related hypertension.
3. It is imperative to early detect BP abnormalities, surrogate biomarkers, and arterial stiffness parameters, to develop effective therapeutic approach to improve cardiovascular outcome in children with CKD.

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