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Research Article

Low urinary citrulline/arginine ratio associated with blood pressure abnormalities and arterial stiffness in childhood chronic kidney disease

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Abstract

Arginine (ARG) and citrulline (CIT) are essential for nitric oxide (NO) synthesis. Their metabolites are interrelated, and involved in blood pressure (BP) control, chronic kidney disease (CKD), and cardiovascular disease (CVD). Although CVD is the leading cause of mortality in CKD, little is known about subclinical CVD in early-stage childhood CKD. Twenty-four–hour ambulatory BP monitoring and arterial stiffness assessment allows the earlier possible detection of subclinical CVD. We investigated whether urinary CIT and ARG metabolites and their ratios are correlated with BP load and vascular abnormalities in children and adolescents with early-stage CKD. We enrolled 55 pediatric patients with mild-to-moderate CKD. Seventy percent (30/43) had at least one out of BP load abnormality on ambulatory BP monitoring, mainly increased asleep systolic BP (SBP) load (40%), asleep SBP or diastolic BP load $>$ 95th percentile (40%), and nocturnal SBP nondipping (35%). Low urinary CIT level and CIT/ARG ratio were associated with BP load abnormalities in children with early CKD. Urinary CIT/ARG ratio was correlated with arterial stiffness, represented as pulse-wave velocity and augmentation index. SBP and diastolic BP loads were negatively correlated with urinary CIT, ARG, asymmetric dimethylarginine (an endogenous NO synthase inhibitor), and CIT/ARG ratio, while positively associated with dimethylamine/asymmetric dimethylarginine ratio and pulse-wave velocity. Early assessments of BP load abnormalities, urinary biomarkers in the CIT-ARG-NO pathway, and arterial stiffness parameters should increase early preventive care toward decreasing hypertension and CV remodeling in pediatric CKD. J Am Soc Hypertens 2016;10(2):115–123.

Keywords: Arginine; chronic kidney disease; hypertension; nitric oxide.

Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in children and adults with chronic kidney disease (CKD). Twenty-four–hour ambulatory blood pressure monitoring (ABPM) is correlated better with cardiovascular outcomes than office blood pressure (BP) in children.[1] Because children with CKD rarely present with cardiovascular events, the detection of subclinical CVD in childhood requires noninvasive measurement of endothelial function, arterial stiffness, and vascular phenotypes. Although there are several techniques available used to detect subclinical CVD, little data are available from children.[2] These vascular assessments include carotid artery intima-media thickness (cIMT), flow-mediated dilatation (FMD), pulse-wave velocity (PWV), augmentation index (AI), and ABPM-derived arterial stiffness index (AASI).[2,3]

Conflict of interest: The authors declare no conflict of interest.

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Urinary and plasma biomarkers are increasingly being investigated for their utility in predicting CVD in patients with CKD.[4] Nitric oxide (NO) deficiency contributes to hypertension, CVD, and CKD.[5] Arginine (ARG) and citrulline (CIT) are two important amino acids that are essential for NO synthesis. ARG is a substrate for NO synthase to generate NO and CIT. ARG can also be metabolized by arginase to generate ornithine, which can be further converted to CIT by ornithine carbamoyltransferase. The body can use CIT to make ARG via the argininosuccinate pathway.[6] ARG can be methylated by protein ARG methyltransferase to produce asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA).[7] ADMA is an endogenous NO synthase inhibitor. Dimethylarginine dimethylaminohydrolase (DDAH) can metabolize ADMA to dimethylamine (DMA) and CIT. Therefore, the metabolites of ARG and CIT are closely interrelated and maintain NO homeostasis (Figure 1).

The kidney is a major site of net de novo ARG synthesis and ADMA metabolism. In advanced CKD stages, plasma CIT and ADMA levels are increased, renal CIT uptake is diminished, and the amount of CIT converted to ARG in the kidney is reduced.[8,9] Nevertheless, plasma ARG levels demonstrate conflicting results in different models of kidney diseases and CVD, confirming the complexity of ARG metabolism.[10] We and others demonstrated that reduced renal ARG availability and increased ADMA levels precede hypertension in young spontaneously hypertensive rats (SHRs).[11,12] We also found that plasma ARG/ADMA ratio and ADMA/SDMA ratio are better markers than each parameter alone (ie, ARG, ADMA) to predict hypertension in young SHRs.[12] In addition, our recent report showed that high plasma CIT/ARG ratio is related to BP load abnormalities in children with early-stage CKD.[13] Although ARG and CIT supplementation have been used therapeutically in CVD and CKD,[14,15] little effort has been made to better understand their metabolites and combined ratios in the development of hypertension and CVD in children with early-stage CKD. Given the important roles of the kidney in amino acid metabolism, de novo ARG synthesis, and ADMA metabolism, we hypothesized that CKD severity would affect the urinary excretion of these amino acids, and that their levels and/or ratios in the urine could predict hypertension in children with mild-to-moderate CKD. Therefore, the aim of this study was to elucidate whether urinary ADMA, DMA, SDMA, ARG, and CIT concentrations and their combined ratios are correlated with abnormalities of BP load and vascular parameters in children and adolescents with early-stage CKD.

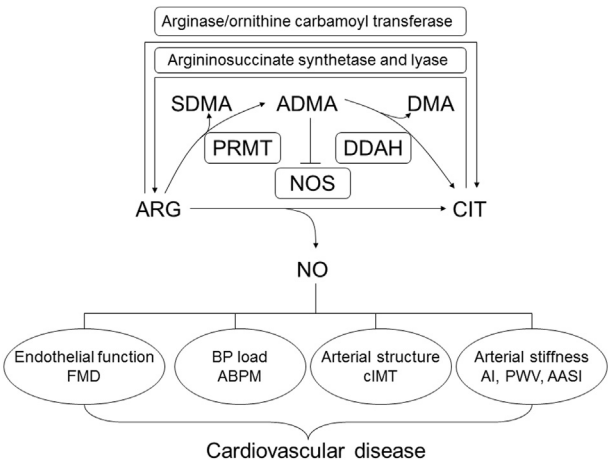

Figure 1. Diagram of the synthesis and metabolism of citrulline (CIT), arginine (ARG), asymmetric dimethylarginine (ADMA), and symmetric dimethylarginine (SDMA) in the nitric oxide (NO) pathway and their relationships to blood pressure load, endothelial function, arterial structure, and arterial stiffness. AASI, ambulatory blood pressure monitoring–derived arterial stiffness index; ABMP, ambulatory blood pressure monitoring; AI, augmentation index; BP, blood pressure; cIMT, carotid artery intima-media thickness; DDAH, dimethylarginine dimethylaminohydrolase; DMA, dimethylarginine; FMD, flow-mediated dilatation; NOS, nitric oxide synthase; PRMT, protein arginine methyltransferase; PWV, pulse-wave velocity.

Materials and Methods

Study Population

We enrolled a total of 55 children and adolescents attending the pediatric clinic at Kaohsiung Chang Gung Memorial Hospital. The study was approved by the Chang Gung Memorial Hospital Institutional Review Board (102-4131C), and followed the 1964 Declaration of Helsinki. Informed consent was obtained from all participants before the study. Renal function was determined by estimated glomerular filtration rate (eGFR) using the Schwartz formula on the basis of body height and creatinine (Cr) level.[16] The eGFR categories were defined according to the K/DIGO guidelines.[17] All participants were assigned to eGFR category G1 (eGFR $\geq$90 mL/min/1.73 m^2), G2 (eGFR 60–89 mL/min/1.73 m^2), or G3a (eGFR 45–59 mL/min/1.73 m^2). The exclusion criteria included current pregnancy, history of congenital heart disease, renal transplantation, and inability to complete major data collection procedures. The following assessments were performed in study participants at the same clinic visit: (1) history taking and physical examination; (2) anthropometry, including height and weight; (3) office BP measurement; and (4) laboratory investigations. Height-for-age and weight-for-age z-scores were calculated with the reference population.[18]