Research Article

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Pulse Wave Velocity, Central Haemodynamic Parameters, and Markers of Kidney Function in Children

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Keywords
Arterial stiffness · Pulse wave velocity · Pulse wave analysis · Cystatin C · Creatinine · Microalbuminurina

Abstract

Objectives: Chronic kidney disease (CKD) is a well-established risk factor for cardiovascular diseases. Studies in adults have demonstrated the association between mildly decreased kidney function or even normal values of markers of kidney function to pulse wave velocity (PWV), a measure of arterial stiffness and a predictor of cardiovascular events. Our study aimed to evaluate associations between markers of CKD, PWV, and central haemodynamic parameters in children and adolescents at risk of subclinical kidney damage.

Methods: 182 children and adolescents with hypertension, obesity, or hypercholesterolaemia (risk factors for subclinical kidney damage) were included in the study. The subjects were subdivided into 4 groups comprising children and adolescents with hypertension (group 1), obesity (group 2), hypercholesterolaemia (group 3), and a group with a combination of risk factors, such as obesity-related hypertension and metabolic syndrome (group 4). The study groups were compared to a group of healthy controls (group 5). PWV was measured by applanation tonometry (SphygmoCor, SCOR-Vx, Sydney, NSW, Australia) and laboratory parameters (serum creatinine, serum cystatin C, and microalbuminurina) were collected. Results: Pearson’s correlation coefficient demonstrated a statistically significant correlation between PWV and serum creatinine in group of all subjects ($r = 0.220$, $p = 0.002$). Further subdivision showed the correlation was significant in group 4 ($r = 0.370$, $p = 0.002$). In group 2 a correlation between PWV and cystatin C was found ($r = -0.535$, $p = 0.009$). In multiple regression analysis of all subjects with PWV as the dependent variable, age and diastolic blood pressure were statistically significant. Correlations between markers of kidney function and central haemodynamic parameters also showed significant correlations between serum creatinine and heart rate (HR) ($r = -0.476$, $p < 0.001$) as well as associated parameters (augmentation index, standardized at HR 75/min, ejection duration, and subendocardial viability ratio).

Conclusions: Our study demonstrated a correlation between serum creatinine and PWV in children with combined risk factors for atherosclerosis and probable subclinical kidney damage. Further prospective research is needed to confirm the findings, and thus the preventive role of PWV determination in paediatric nephrology.

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Introduction

Cardiovascular diseases (CVDs), such as ischaemic heart disease and stroke, have been the leading cause of death globally in the last 15 years [1]. Along with traditionally known risk factors for CVD, chronic kidney disease (CKD) has also been found an independent risk factor for cardiovascular morbidity and mortality. Proteinuria, elevated serum creatinine, and reduced glomerular filtration rate are proven to be significant predictors of CVD [2, 3]. Arterial stiffness increases with a decrease in renal function or with proteinuria, independent of other risk factors [4]. Studies in children with CKD have reported increased arterial stiffness in children with advanced CKD, on dialysis, and after kidney transplantation [5]. However, recent studies have shown that even mildly decreased kidney function is an independent risk factor for CVD outcome [6]. Increased arterial stiffness indicates a pathological state of vascular damage and is directly associated with atherosclerosis, which starts in childhood [2, 7]. One of the possible methods to assess vascular elasticity is pulse wave velocity (PWV) measurement. It is closely related to the stiffness of large arteries and is a strong predictor of cardiovascular events in adults [2]. In children, increased PWV, indicating a stiffer artery, has been associated with classical CVD risk factors, such as hypertension, obesity, and hypercholesterolaemia [8, 9]. Assessing arterial stiffness with PWV in adults has shown that cystatin C could be independently related to PWV even in subjects with normal serum creatinine [7]. In the paediatric population, several studies have demonstrated the association between PWV and hypertension, obesity, and diabetes [10, 11]; however, there are very limited data assessing the relation between PWV and markers of kidney function. Schaefer et al. [12] demonstrated an increased PWV in children with CKD, while subendocardial viability ratio (SEVR) has been associated with albuminuria in adults with CKD [13]. Our study aimed to evaluate whether serum cystatin C, creatinine, and microalbuminuria could independently be related to PWV and central haemodynamic parameters in children and adolescents in the absence of proven CKD.

Material and Methods

Subjects

A total of 182 children and adolescents were included in the study. Subjects were admitted to our hospital for additional diagnostic workup of cardiovascular risk factors and evaluation of kidney function. They were diagnosed according to diagnostic guidelines and age-dependent cut-off values [14–17]. The data were analysed retrospectively. Subjects with measured PWV and complete laboratory workup were selected. The study of PWV measurement was approved by Institutional Ethics Committee, and laboratory investigations were performed as part of a routine follow-up. We examined our PWV measurements and included all children and adolescents with hypertension (group 1, N = 72), obesity (group 2, N = 23), hypercholesterolaemia (group 3, N = 17), and combined cardiovascular risk factors, such as obesity-related hypertension and metabolic syndrome (group 4, N = 70) for whom all necessary measurements and laboratory data were available. The study groups were compared to healthy individuals (group 5, N = 20).

Data Collection

PWV was measured by arterial applanation tonometry (Sphygmocor, SCOR-Vx, Sydney, NSW, Australia). All measurements were performed by the same trained investigator with good intra-observer reliability. Before the measurement, each subject’s height, weight, blood pressure, and the arterial path length between the 2 recording sites (e.g., radial and carotid arteries) were measured. Next, a pressure tonometer was used to transcutaneously record the pressure pulse waveform. An ECG signal provided a timing reference for the software to be able to calculate PWV. Pulse wave analysis was then performed using the same software, which enabled detailed evaluation of central haemodynamic parameters with emphasis on central blood pressure, SEVR, ejection duration (ED), and augmentation index (Alx) measurement. Alx is, like PWV, a measure of systemic arterial stiffness derived from the ascending aortic pressure waveform. It is calculated from pulse wave reflection pressures as the augmentation pressure divided by the pulse pressure [18, 19].

The following data were collected for each participant: age, height, weight, body mass index (BMI), systolic blood pressure (SP), diastolic blood pressure (DP), serum cystatin C and creatinine, urinary microalbumin/creatinine ratio, PWV, and central haemodynamic data. The glomerular filtration rate for creatinine and cystatin C was calculated using the creatinine-based “Bedside Schwartz” equation (estimated glomerular filtration rate [eGFR] = 0.413 × [height/creatinine]) [20] and the cystatin C-based equation (eGFR = 70.69 × [cystatin C]^{-0.931}) [21].

SPSS Statistics (IBM, version 22) was used for statistical analyses. Multiple regression analysis, Pearson’s correlation, and the ANOVA test were used. A value of p < 0.05 was considered statistically significant.

Results

Table 1 shows the basic characteristics of the studied groups. Results are shown as the median (Q1 and Q3) due to non-homogeneous groups. The groups were additionally compared using the ANOVA test.

Multiple regression analysis, presented in Table 2, included age, BMI (height and weight were excluded due to collinearity with BMI), SP, DP, serum cystatin C, serum creatinine and the urinary microalbumin/creatinine ratio. Adjusted $R^2$ for the model was 0.213 with a standard
### Table 1. Characteristics of studied groups and comparison of variables using the ANOVA test

| Variables                        | Group 1            | Group 2            | Group 3            | Group 4            | Group 5            | p value  |
|----------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|----------|
| Age, years                       | 16 (14, 17)        | 12 (9, 16)         | 13 (5, 15)         | 13 (10, 16)        | 15 (9, 17)         | <0.001   |
| Height, cm                       | 174 (160, 180)     | 166 (140, 175)     | 152 (121, 170)     | 164 (144, 174)     | 164 (142, 175)     | <0.001   |
| Height, SDS                      | 0.56 (−0.03, 0.86) | 0.19 (−0.06, 0.62) | −0.50 (−2.00, 0.35)| 0.09 (−0.86, 0.58) | −0.1 (−0.95, 0.59) | <0.001   |
| Weight, kg                       | 66.5 (54, 76)      | 82 (48, 97)        | 45 (23, 70)        | 79 (53, 99)        | 59 (35.3, 70.8)    | <0.001   |
| Weight, SDS                      | −0.03 (−0.51, 0.29)| 0.51 (−0.74, 1.07) | −0.83 (−1.67, 0.02)| 0.43 (−0.54, 1.18) | −0.31 (−1.21, 0.09)| <0.001   |
| BMI, kg/m²                       | 22.3 (19.77, 23.53)| 29.1 (24.9, 32.8)  | 18.2 (16.25.5)     | 27.5 (23.3, 32.5)  | 19.85 (16.8, 23.99)| <0.001   |
| BMI SDS                          | −0.32 (−0.74, −0.19)| 0.62 (0.01, 1.18)  | −0.83 (−1.3, 0.10) | 0.44 (−0.22, 1.14) | −0.68 (−1.18, −0.12)| <0.001   |
| SP, mm Hg                        | 136 (128, 145)     | 119 (115, 125)     | 116 (105, 129)     | 133 (120, 143)     | 120 (114, 126)     | <0.001   |
| SP, SDS                          | 0.29 (−0.12, 0.86) | −0.64 (−0.87, −0.29)| −0.86 (−1.48, −0.09)| 0.09 (−0.58, 0.75) | −0.66 (−0.93, −0.25)| <0.001   |
| DP, mm Hg                        | 79 (72, 88)        | 68 (65, 73)        | 73 (64, 83)        | 80 (72, 88)        | 70 (67, 73)        | <0.001   |
| DP, SDS                          | 0.06 (−0.46, 0.87) | −0.79 (−1.03, −0.37)| −0.43 (−1.12, 0.41)| 0.14 (−0.48, 0.87) | −0.68 (−0.87, −0.39)| <0.001   |
| PWV, m/s                         | 6.45 (5.9, 7.2)    | 5.6 (4.7, 6.4)     | 5.9 (4.9, 7.3)     | 6.1 (5.1, 6.9)     | 5.9 (5.2, 6.7)     | 0.001    |
| Serum cystatin C, mg/L           | 0.78 (0.7, 0.84)   | 0.74 (0.68, 0.89)  | 0.77 (0.67, 0.95)  | 0.77 (0.7, 0.83)   | 0.83 (0.67, 0.94)  | 0.447    |
| Serum creatinine, micromol/L     | 69 (58, 80)        | 60 (47, 72)        | 54 (36, 72)        | 58 (46, 74)        | 55 (46, 72)        | <0.001   |
| Urinary M/C, mg/g                | 7 (4, 10)          | 8 (6, 15)          | 10 (4, 16)         | 7 (3, 12)          | 7 (5, 14)          | 0.133    |
| eGFR for creatinine, mL/min/1.73 m² | 92 (79, 105) | 101 (84, 109) | 109 (86, 126) | 102 (85, 121) | 98 (92, 112) | 0.011 |
| eGFR for cystatin C, mL/min/1.73 m² | 89 (83, 99) | 94 (79, 101) | 90 (74, 102) | 90 (84, 99) | 84 (75, 103) | 0.887 |
| HR, /min                         | 77 (67, 87)        | 76 (62, 87)        | 85 (74, 103)       | 81 (69, 95)        | 80 (68, 87)        | 0.050    |
| Alx75, %                         | −4 (−17, 6)        | −15 (−28, −5)      | 1 (−17, 11)        | −6 (−17, 10)       | −22 (−28, −6)      | 0.008    |
| SEVR, %                          | 159 (140, 181)     | 149 (121, 168)     | 121 (105, 153)     | 139 (124, 168)     | 133 (124, 162)     | 0.007    |
| ESP, mm Hg                       | 106 (99, 118)      | 92 (88, 97)        | 100 (88, 108)      | 105 (98, 113)      | 107 (101, 115)     | <0.001   |
| CSP, mm Hg                       | 114.5 (104, 123)   | 101 (95, 110)      | 101 (92, 112)      | 111 (102, 119)     | 116 (112, 122)     | 0.001    |
| CDP, mm Hg                       | 94 (86, 100)       | 83 (77, 88)        | 88 (80, 93)        | 93 (86, 100)       | 69 (66, 73)        | <0.001   |
| CPP, mm Hg                       | 19 (13, 25)        | 21 (17, 24)        | 16 (10, 21)        | 16 (13, 22)        | 50 (39, 57)        | <0.001   |
| CMP, mm Hg                       | 101 (91, 108)      | 88 (83, 95)        | 94 (84, 98)        | 100 (92, 106)      | 85 (80, 92)        | <0.001   |
| ED, %                            | 34 (32, 38)        | 34 (30, 38)        | 40 (35, 45)        | 38 (33, 41)        | 38 (32, 39)        | <0.001   |

The results are presented as the median (Q1 and Q3). SDS, standard deviation score; BMI, body mass index; PWV, pulse wave velocity; eGFR, estimated glomerular filtration rate; M/C, microalbumin/creatinine; HR, heart rate; Alx75, augmentation index at HR of 75/min; SEVR, subendocardial viability ratio; ESP, end-systolic pressure; CSP, central systolic pressure; CDP, central diastolic pressure; CPP, central pulse pressure; CMP, central mean pressure; ED, ejection duration; SP, systolic blood pressure; DP, diastolic blood pressure.
error of the estimate of 1.08. Age and DP were shown to be statistically significant in the model.

PWV significantly correlated with age, height, weight, SP, DP, serum creatinine, and central pressure (central end-systolic, systolic, diastolic, and mean pressure) but not with BMI, serum cystatin C, microalbuminuria, eGFR for creatinine and cystatin C, heart rate (HR), Alx75, central pulse pressure, and ED. The correlation with SEVR was on the border of statistical significance. Correlations are presented in Table 3.

Correlation tests between PWV and markers of kidney function were performed, presented in Table 4. In groups 4 and 5, creatinine significantly positively correlated with PWV, although the statistical significance was lower in group 5. In the group 2, cystatin C significantly negatively correlated with PWV.

In Table 5, correlations between central haemodynamic parameters and markers of kidney function are presented. The results show significant correlations between serum creatinine and HR, Alx75, SEVR, ESP, central pressures, and ED.

**Discussion**

In our study, we focused on possible associations between markers of kidney function and cardiovascular risk predictors in children and adolescents. We recruited children with cardiovascular risk factors and found a correlation between PWV, a marker of early atherosclerosis in children, and serum creatinine, a marker of kidney function. Paediatric studies indicate an association between CKD and impaired endothelial function in children [22], with CVDs being the most common cause of mortality [23]. However, cardiovascular risk in children at risk of subclinical kidney damage with a normal glomerular filtration rate has yet to be determined. There are several potential mechanisms to explain the link between kidney function and arterial stiffness, such as promoting arterial stiffness through its effect on hypertension and salt retention. The latter may also express a direct trophic effect on the vasculature, and sodium may modify vascular tone by affecting the sympathetic nervous system. Experimentally, kidney-induced changes in the viscoelastic arterial properties were observed independently of the presence of atherosclerosis. Kidney disease may also cause an increase in other risk factors for arterial stiffness. Finally, it is possible that increased arterial stiffness leads to kidney damage, creating a vicious cycle [6].

Bartz et al. [24] demonstrated the link between the urine albumin-to-creatinine ratio with a direct measure of endothelial dysfunction in non-diabetic children. Other recently published studies have investigated vascular stiffness in children with CKD [12, 25]. Cardiovascular
phenotypes in children with CKD have also been assessed [12].

In our study, we included children and adolescents with possible subclinical kidney dysfunction due to hypertension, obesity, or hypercholesterolaemia, which are risk factors for early atherosclerosis and subsequent early kidney damage [26]. Urinary albumin excretion is a result of increased vascular permeability related to endothelial damage, and in adults, there is an association with CVD, even at levels below the threshold of microalbuminuria [24]. Cystatin C has also been associated with PWV in subjects with normal creatinine and has been demonstrated as a powerful and independent risk factor for CVD outcomes, even in mildly decreased kidney function [6, 7].

In our study, a correlation test confirmed the association between PWV and serum creatinine for all included patients. This association was mainly seen in group 4, where multiple risk factors were present, indicating the predominant cardiovascular risk and potential renal risk. In adults, increased stiffness, as measured by PWV, has already been associated with reduced creatinine clearance in subjects with mild-to-moderate renal insufficiency. Increased arterial stiffness has been proven to be the vascular hallmark of subjects with end-stage renal disease independently of age, blood pressure, and standard risk factors [27]. Ohya et al. [28] showed a similar association in a low-risk adult population who attended a health check programme. In children, it could be argued that like PWV, serum creatinine also rises with age, but in that case, the same correlations in all groups would be expected. There was a less significant correlation in the control group, possibly due to the effect of muscle mass and small sample size. Cystatin C is believed to be less affected by growth changes; however, its concentration varies significantly according to age, gender, and pubertal status [29]. In our study, it correlated negatively with PWV only in group 2. The possible association between kidney function and PWV should be additionally researched with methods that are not affected by growth.

Albuminuria, a potential marker for atherosclerosis, causes glomerular damage and seems to be associated with glomerular endothelial injury [13]. Its role was not

### Table 4. Correlations between PWV and markers of kidney function within groups

| Group  | PWV and serum cystatin C (r, p value) | PWV and serum creatinine (r, p value) | PWV and microalbuminuria (r, p value) |
|--------|---------------------------------------|--------------------------------------|--------------------------------------|
| 1      | −0.036, 0.765                         | −0.058, 0.630                        | 0.011, 0.927                         |
| 2      | −0.535, 0.009                         | 0.088, 0.691                         | 0.183, 0.404                         |
| 3      | −0.320, 0.210                         | 0.005, 0.984                         | 0.218, 0.400                         |
| 4      | −0.088, 0.468                         | 0.370, 0.002                         | −0.041, 0.736                        |
| 5      | 0.207, 0.381                          | 0.508, 0.022                         | −0.069, 0.772                        |

PWV, pulse wave velocity.

### Table 5. Correlations between central haemodynamic parameters and markers of kidney functions

| Central haemodynamic parameters | Serum cystatin C (r, p value) | Serum creatinine (r, p value) | Microalbuminuria (r, p value) |
|---------------------------------|-------------------------------|-----------------------------|-------------------------------|
| HR, /min                        | −0.059, 0.402                 | −0.467, < 0.001             | −0.004, 0.658                |
| Alx75, %                        | −0.110, 0.120                 | −0.175, 0.0013              | −0.033, 0.644                |
| SEVR, %                         | 0.075, 0.490                  | 0.541, < 0.001              | −0.008, 0.912                |
| ESP, mm Hg                      | −0.046, 0.515                 | 0.305, < 0.001              | 0.084, 0.236                 |
| CSP, mm Hg                      | 0.009, 0.897                  | 0.320, < 0.001              | 0.127, 0.070                 |
| CDP, mm Hg                      | −0.080, 0.258                 | 0.254, < 0.001              | 0.103, 0.146                 |
| CPP, mm Hg                      | −0.080, 0.256                 | 0.094, 0.184                | 0.038, 0.590                 |
| CMP, mm Hg                      | −0.058, 0.413                 | 0.305, < 0.001              | 0.127, 0.072                 |
| ED, %                           | −0.070, 0.322                 | −0.527, < 0.001             | −0.009, 0.903                |

r, Pearson’s coefficient; p, significance; HR, heart rate; Alx75, augmentation index at HR of 75/min; SEVR, subendocardial viability ratio; ESP, end-systolic pressure; CSP, central systolic pressure; CDP, central diastolic pressure; CPP, central pulse pressure; CMP, central mean pressure; ED, ejection duration.
confirmed in our study; however, it should be studied prospectively and on a larger sample.

Multiple regression analysis, which included all collected variables, demonstrated only age and DP as statistically significant independent factors. PWV correlated significantly with central blood pressure, which was expected due to the well-known effect of hypertension on arterial stiffness.

The other aspect of our study was to evaluate markers of kidney function in relation to central haemodynamic parameters, especially SEVR and ED, which are significantly associated with levels of albuminuria in adults with CKD [13]. Our results did not confirm these associations. Surprisingly, serum creatinine significantly negatively correlated with HR, Alx75, and ED and positively with SEVR, which were the opposite of what we expected. In adults, resting HR is associated with higher creatinine levels [30]. The explanation is probably based on the physiological development of children, with decreasing HR and increasing creatinine levels with growth, which results in the above-mentioned correlation. Our results also showed a significant correlation of serum creatinine with age, height, and weight, which is consistent with previous studies. The same would be expected for blood pressure; however, our study population included many hypertensive patients, which concealed the expected correlation. Other correlating central haemodynamic parameters are partly dependent on the HR, so we are of opinion that their correlation is also a consequence of the physiological state. Murakami et al. [19] also showed a positive relationship between SEVR and age in children. Our prediction is supported by the fact that the results of other kidney function markers do not show an association with central haemodynamic parameters.

The main disadvantages of our study are the small sample size and the retrospective data analysis of kidney markers. To avoid further reducing the statistical power, we did not analyse subgroups according to their age. However, we believe that our results justify further research in this field. The study could also be further improved by adding another reference method for studying subclinical atherosclerosis or kidney function that is not affected by growth and development.

Conclusions

The aim of our study was to investigate whether there is a connection between PWV, a measure of arterial stiffness, central haemodynamic parameters, and markers of kidney function, serum cystatin C, serum creatinine, and the albumin/creatinine ratio in children and adolescents who are at risk of subclinical kidney damage. We were able to demonstrate a connection between PWV and serum creatinine in children and adolescents at greater risk of subclinical kidney damage, especially in those with multiple cardiovascular risk factors, indicating both their cardiovascular and renal risk. Further research with a larger sample is needed to confirm the association and hence the role of PWV determination in preventive paediatric nephrology.

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Statement of Ethics

All the data were collected during the study, which was approved by Institutional Ethics Committee of University Medical Centre Maribor (UKC-MB-KME-25/16). Subjects’ parents or guardians have given their written informed consent. We also requested for an addendum to the basic application for retrospective data analysis. The study was conducted in accordance with the provisions of the Declaration of Helsinki, the Oviedo Convention, and the principles of the Slovenian Code of Medical Deontology.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

All authors read and approved the final manuscript. N.M.V. planned the study, collected the patients, supervised and guided the study, revised the data analysis and the written manuscript, and approved the version to be published. M.M. planned the study, measured the patients, analysed and interpreted the data, and wrote the manuscript.

Data Availability Statement

All the data are available from the corresponding author upon reasonable request.
References

1. World Health Organization. Top ten causes of death. 2020 Dec 9 [Cited 2017 May 22]. Available from: http://www.who.int/media-centre/factsheets/fs310/en/.

2. Odaire M, Tomiyama H, Matsumoto C, Yamada J, Yoshihara M, Shinya K, et al. Association of serum cystatin C with pulse wave velocity, but not pressure wave reflection, in subjects with normal renal function or mild chronic kidney disease. Am J Hypertens. 2010;23:967–73.

3. Irie F, Iso H, Sairenchi T, Fukasawa N, Yamagishi K, Ikeda S, et al. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. Kidney Int. 2006;69:1264–71.

4. Ohya Y, Iseki K, Iseki C, Miyagi T, Kinjo K, Takishita S. Increased pulse wave velocity is associated with low creatinine clearance and proteinuria in a screened cohort. Am J Kidney Dis. 2006;47:790–7.

5. Azukaitis K, Januskauskiene A, Schaefer F, Shroff R. Pathophysiology and consequences of arterial stiffness in children with chronic kidney disease. Pediatr Nephrol. 2021;36(7):1683–95.

6. Madero M, Wassel CL, Peralta CA, Najjar SS, Sutton-Tyrrell K, Fried L, et al. Cystatin C associates with arterial stiffness in older adults. J Am Soc Nephrol. 2009;20:1086–93.

7. Song SH, Kwas JS, Kim YJ, Lee HS, Rhee H, Lee DW, et al. Serum cystatin C is related to pulse wave velocity even in subjects with normal serum creatinine. Hypertens Res. 2008;31:1895–902.

8. Kulsum-Mecczi N, Goss C, Kozel BA, Garbutt JM, Schechtman KB, Dharndiharka VR. Effects of obesity and hypertension on pulse wave velocity in children. J Clin Hypertens. 2017;19:221–6.

9. Riggio S, Mandraffino G, Sardo MA, Judicello R, Camarda N, Imbalzano E, et al. Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hypercholesterolemic children. Eur J Clin Investig. 2010;40:250–7.

10. Im JA, Lee JW, Shim YJ, Lee HR, Lee DC. Association between brachial-ankle pulse wave velocity and cardiovascular risk factors in healthy adolescents. J Pediatr. 2007;150:247–51.

11. Haller MJ, Samyn M, Nichols WW, Brusko T, Wasserman C, Schwartz RF, et al. Radial artery tonometry demonstrates arterial stiffness in children with type 1 diabetes. Diabetes Care. 2004;27:2911–7.

12. Shafer F, Doyon A, Azukaitis K, Bayazit A, Canpolat N, Duzova A, et al. Cardiovascular phenotypes in children with CKD: the 4C Study. Clin J Am Soc Nephrol. 2017;12:19–28.

13. Elkat R, Bevc S, Hojs N, Knehtl M, Dvoršak B, Hojs R. Albuminuria is associated with subendocardial viability ratio in chronic kidney disease patients. Kidney Blood Press Res. 2015;40(6):565–74.

14. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34:1887–920.

15. Hebebrand J, Holm JC, Woodward E, Baker JL, Blak E, Durrer Schult D, et al. A Proposal of the European Association for the Study of Obesity to improve the ICD-11 diagnostic criteria for obesity based on the three dimensions etiology, degree of adiposity and health risk. Obes Facts. 2017;10:284–307.

16. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease: executive summary complete appendix to guidelines available at Endocr Pract. 2017;23(4):479–97.

17. Welte P, Weirather-Blüher S. Metabolic syndrome in children and adolescents: diagnostic criteria, therapeutic options and perspectives. Curr Obes Rep. 2019;8(4):472–9.

18. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ, et al. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol. 2000;525 Pt 1:263–70.

19. Murakami T, Takeda A, Taka K, Tateno S, Kawase Y, Niwa K. The cardiac blood supply-workload balance in children. Heart Vessels. 2015;30:626–31.

20. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4:1832–43.

21. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharndiharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82:445–53.

22. Kari JA, Donald AE, Vallance DT, Bruckdorfer KR, Leone A, Mullen MJ, et al. Physiology and biochemistry of endothelial function in children with chronic renal failure. Kidney Int. 1997;52:468–72.

23. Khandelwal P, Murugan V, Haji S, Lakshmy R, Sinha A, Hari P, et al. Dyslipidemia, carotid intimamedia thickness and endothelial dysfunction in children with chronic kidney disease. Pediatr Nephrol. 2016;31:1313–20.

24. Bartz SK, Caldas MC, Tomas A, Krishnamurthy R, Bacha F. Urine albumin-to-creatinine ratio: a marker of early endothelial dysfunction in youth. J Clin Endocrinol Metab. 2015;100:3393–9.

25. Savant JD, Betoko A, Meyers KE, Mitsnefes M, Flynn JT, Townsend RR, et al. Vascular stiffness in children with chronic kidney disease. Hypertension. 2017;69:863–9.

26. Sorof J, Daniels S. Obesity hypertension in children: a problem of epidemic proportions. Hypertension. 2002;40:441–7.

27. Mourad JJ, Pannier B, Blacher J, Rudnichi A, Benetos A, London GM, et al. Creatinine clearance, pulse wave velocity, carotid compliance and essential hypertension. Kidney Int. 2001;59:1834–41.

28. Ohya Y, Iseki K, Iseki C, Miyagi T, Kinjo K, Takishita S. Increased pulse wave velocity is associated with low creatinine clearance and proteinuria in a screened cohort. Am J Kidney Dis. 2006;47:790–7.

29. Ziegler NS, Vogel M, Müller E, Tremel N, Jurkutat A, Löffler M, et al. Cystatin C serum levels in healthy children are related to age, gender, and pubertal stage. Pediatr Nephrol. 2019;34:449–57.

30. Böhmer M, Schumacher H, Schmiedre RE, Mann JF, Teo K, Lonn E, et al. Resting heart rate is associated with renal disease outcomes in patients with vascular disease: results of the Ontarget and Transcend studies. J Intern Med. 2015;278:38–49.