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Article

Arterial Stiffness and Chronic Kidney Disease Progression in Children

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Abstract

Background and objectives CKD has been linked to increased arterial stiffness in adults, but data in children with CKD remain conflicting. We aimed to investigate the longitudinal dynamics and determinants of pulse wave velocity in children with CKD and its association with CKD progression.

Design, setting, participants, & measurements We performed an analysis of the Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) study, which prospectively followed children aged 6–17 years with CKD stages 3–5. Follow-up was censored at the time of KRT initiation. Two separate analyses were performed: with absolute pulse wave velocity (primary outcome) and with pulse wave velocity standardized to height (*z* score; restricted to participants ≤17 years) as a sensitivity analysis.

Results In total, 667 patients with a mean baseline eGFR of 27 ml/min per 1.73 m^2 were included. Pulse wave velocity above the 95th percentile was observed in 124 (20%) patients at baseline. Absolute pulse wave velocity increased gradually over the median follow-up of 2.7 (interquartile range, 0.7–4.4) years, whereas pulse wave velocity *z* score remained relatively stable. Absolute pulse wave velocity over time associated with time; older age; higher mean arterial pressure, LDL cholesterol, and albuminuria; and lower ferritin. Pulse wave velocity *z* score ($n=628$) was associated with the same variables and additionally, with higher diastolic BP *z* score, lower height *z* score, younger age, and girls. Of 628 patients, 369 reached the composite end point of CKD progression (50% eGFR loss, eGFR <10 ml/min per 1.73 m^2, or the start of KRT) during a median follow-up of 2.4 (interquartile range, 0.9–4.6) years. Pulse wave velocity *z* score did not associate with CKD progression by univariable or multivariable proportional hazard analysis correcting for the established predictors eGFR, proteinuria, and BP.

Conclusions Pulse wave velocity is increased in children with CKD but does not associate with eGFR or CKD progression.

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Introduction

Children with CKD represent the pediatric population with the highest cardiovascular risk (1). CKD induces clinically silent but progressive remodeling of medium- and large-sized arteries. Alterations, such as calcifications or osteoblastic transformation of the tunica media, have been reported even in young children with advanced CKD (2) and may lead to accelerated arterial stiffening (3). Large studies involving adults with CKD also demonstrated a direct relationship between increased arterial stiffness and CKD progression (4,5).

Studies in children with CKD have thus far reported conflicting evidence about the prevalence of arterial stiffening (6–8). A range of risk factors was suggested to contribute to arterial stiffening during childhood, but a comprehensive description of the risk profile and association with CKD progression in children is lacking. The primary aim of our analysis was to investigate the evolution and risk factors for arterial stiffening by measuring pulse wave velocity (PWV) in a large prospective cohort of children with predialysis CKD. As a secondary aim, we sought to explore whether PWV is associated with CKD progression.

Materials and Methods

Study Design and Setting

The analysis included patients enrolled in the Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) study. The 4C study is a prospective cohort study that enrolled children with CKD from 55 pediatric nephrology centers across 12 European countries during 2010–2011 and followed them until 2018. The study included children aged 6–17

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years old with eGFR between 10 and 60 ml/min per 1.73 m^2 not on KRT.

The patients were followed with 6-month visits that included data collection, clinical examination, and collection of laboratory samples. Every 12 months, measurements of PWV were performed by centrally trained regional coordinators. Details of the study protocol have been summarized elsewhere (9).

All patients with at least one PWV measurement while not on KRT and with eGFR <60 ml/min per 1.73 m^2 were included. If the inclusion criteria were met at a visit that occurred later than the baseline visit, the first visit meeting eligibility criteria were set as the new baseline. Patient follow-up was censored at the time of KRT initiation.

Data Collection and Definitions

Carotid-femoral PWV was measured using a validated oscillometric device, the Vicorder (SMT Medical), according to a standardized procedure (details are in Supplemental Material) (10). The pulse wave travel distance was calculated as (suprasternal notch to umbilicus) + (umbilicus to femoral) – (suprasternal notch to carotid). The mean value of three consecutive PWV readings was used for the analysis, and then, the pulse wave velocity standardized to height (PWVz) was calculated by sex-specific z scores (11). PWVz was used for the primary analysis on the basis of previous data that standardization to age in children with growth restriction may lead to underestimation of PWV values (12, 13). PWV values above the 1.645 z score (corresponding to the 95th percentile) were considered elevated.

Height and body mass index (BMI) were standardized by calculating z scores using World Health Organization reference data. Obesity, overweight, and underweight were defined as BMI z scores of >2, >1, and <−2, respectively (14). Patients were considered born small for gestational age if their birth weight or height was below the 10th percentile.

BP was measured with locally available oscillometric devices validated for the use in pediatric patients using appropriately sized cuffs, and the mean value of three consecutive BP measurements (with at least 1-minute intervals) in the resting state was used. Mean arterial pressure was calculated as diastolic BP + (systolic BP – diastolic BP)/3. Systolic and diastolic BP values were age, sex, and height standardized (15). BP z scores for patients older than 17 years were calculated using the maximum age for which reference data are available because of inappropriate exponentiation using actual age. Hypertension was defined as systolic and/or diastolic BP >95th percentile (16).

Kidney disease etiology was classified as described in Supplemental Table 1. Serum creatinine was measured by the immunoenzymatic assay, and eGFR was calculated using the updated Schwartz equation (17). CKD progression was defined as the time to a composite event of 50% reduction in eGFR, eGFR <10 ml/min per 1.73 m^2, or the start of KRT, whichever occurred first. If 50% reduction in eGFR occurred between two study visits, interpolation was used to determine the time point of the event.

All blood and urine samples were analyzed in a central laboratory (except for hemoglobin, intact parathormone, serum bicarbonate, and ferritin). Proteinuria was defined as urinary albumin-creatinine ratio (UACR) >30 mg/g, and nephrotic-range proteinuria was defined as UACR >2200 mg/g.

Statistical Analyses

Continuous variables are summarized by mean (SD) or median (interquartile range [IQR]), and categorical variables are summarized by frequencies. Continuous variables were checked for normal distribution by visual inspection and comprehensive summary statistics. Non-normally distributed variables were log transformed. Sex-, age-, and/or height-dependent variables were standardized to calculating z scores by the LMS method or using published regression equations (11,14,15,18).

Linear regression analysis was performed to assess the association of variables with PWV at baseline (details can be found in Supplemental Material). As 25(OH)-vitamin D3 levels were only measured in a subgroup, it was only considered in supplementary analyses.

The main interest of this paper was determining associations of variables with PWV over time. Because of a lack of reference data for z-score calculation of PWV beyond the age of 17 years, modeling absolute PWV was selected as the primary analysis, including all observations. As a sensitivity analysis, a model of PWVz (restricted to observations with age ≤17 years) was built. The longitudinal change since baseline PWV recording was visualized by a scatterplot of the observed data together with the predicted mean PWV trajectory with a 95% confidence band. The prediction was on the basis of a generalized additive mixed effects model with a penalized spline fixed effect for time to account for the possible nonlinear effect of time and patient-individual random intercept and slopes.

To determine the association of time-dependent explanatory variables with the outcomes of interest (absolute PWV and PWVz), multivariable linear mixed effects models with time as the fixed effect and patient-individual random intercepts and slopes were built. To account for potential nonlinear effects of time, $time^2$ was included additionally as a fixed effect, and the model with the lower Akaike information criterion was taken as the final model. Variable selection for longitudinal models was on the basis of the results of baseline analysis and clinical judgment. The same variables were used in both PWV models except for height and diastolic BP, where absolute values were used in the model for PWV and standardized values for PWVz. First, constant effects over time of the explanatory variables were modeled, and in a second step, time interactions were included for all variables to account for potential changes in the effects over time.

Multiple imputation with a multiple imputation by chained equations algorithm was used to impute missing data of the explanatory variables using appropriate linear mixed effects models and all available covariates as predictors to minimize bias. More details are in Supplemental Material.

The Cox proportional hazard model with PWVz at baseline and as a time-varying variable along with known CKD progression predictors was built to evaluate the association of PWVz with the composite end point of CKD progression. Participants with age >17 years at baseline were

excluded from this analysis due to the missing reference values for PWV. Kaplan–Meier survival curves are shown stratified by tertiles of PWVz, and the log rank test was used to compare kidney survival.

This is an exploratory analysis resulting in descriptive *P* values, which were not adjusted for multiple testing. A two-sided *P* value of 0.05 was considered statistically significant in the presentation of results. Statistical analysis was performed using SAS Software version 9.4 (SAS Inc., Cary, NC) and R version 3.2.2.

Results

Baseline Characteristics

A total of 667 patients (n=437, 66% boys; mean age 12±3 years) with 2295 visits meeting the eligibility criteria (Figure 1) were included into the analysis. The predominant primary kidney disease was congenital anomalies of kidney and urinary tract (n=464; 70%). Mean eGFR at baseline was 27±12 ml/min per 1.73 m^2, and 37%, 48%, and 15% were in CKD stages 3–5, respectively. The majority of children were proteinuric (n=583; 87%), 188 (28%) were hypertensive, and 229 (34%) were receiving antihypertensive medications. Most of the children had normal BMI, and 122 (18%) and 34 (5%) were overweight and obese, respectively. The median height z score was −1.26 (IQR, −2.08 to −0.45), and 202 (30%) had short stature.

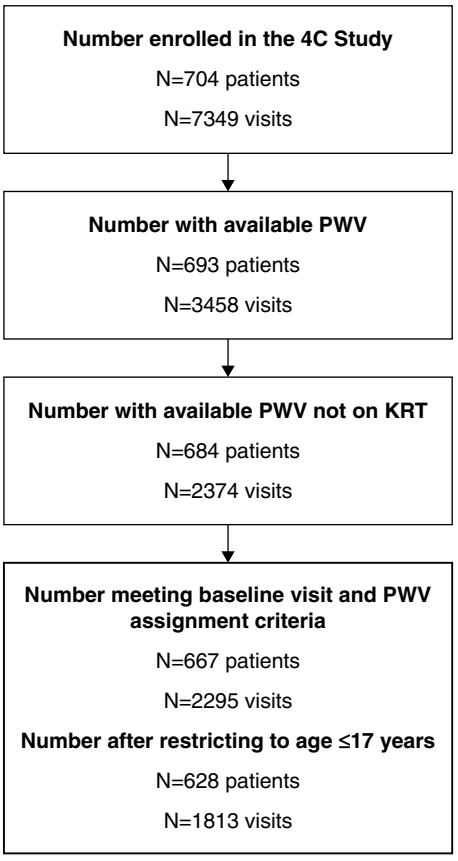

Figure 1. | Patient and observation selection flow chart. 4C, Cardiovascular Comorbidity in Children with Chronic Kidney Disease; PWV, pulse wave velocity.

The main clinical characteristics of the study population at baseline are summarized in Table 1.

Pulse Wave Velocity and Its Correlates at Baseline

Mean PWV at baseline was 4.9±0.8 m/s, and median PWVz was 0.26 (IQR, −0.75 to 1.4). Overall, 124 (20%) and 64 (10%) of 628 patients who were ≤17 years at baseline had PWV above the 95th and 99th percentiles, respectively.

Univariable regression was performed to determine factors associated with PWV at baseline (Supplemental Table 2). In the multivariable regression model after stepwise selection (n=604), higher absolute PWV was associated with older age, higher mean arterial pressure, lower log ferritin, and lower HDL cholesterol (Table 2). This model explained approximately 30% of PWV variability (28% explained by age and mean arterial pressure). After inclusion of log 25(OH)-vitamin D3 into the multivariable regression, it remained in the final model, whereas sample size was reduced due to missing values (Supplemental Tables 2 and 3).

Repeating the analysis for PWVz in the subgroup of patients with age ≤17 years and available 25(OH)-vitamin D3 levels showed associations with younger age, lower height z score, higher diastolic BP z score, lower log-transformed ferritin, and lower log-transformed 25(OH)-vitamin D3 levels (eligible variables were standardized to z scores) (Supplemental Tables 4 and 5).

Longitudinal Changes and Time-Varying Associations of Pulse Wave Velocity

Median follow-up was 2.7 years (IQR, 0.7–4.4 years), with a maximum follow-up of 8.7 years. The distribution of the number of observations per participant is presented in Supplemental Figure 1. Data for at least one variable were missing in 11% (of 667) and 24% (of 2295) of observations at baseline and during follow-up, respectively (Supplemental Figures 2 and 3).

Absolute PWV increased gradually, whereas PWVz remained relatively stable (Figure 2). Absolute PWV over time was nonlinearly associated with time and showed time-stable associations with older age, higher mean arterial pressure, higher LDL cholesterol, higher log UACR, and lower log ferritin (Supplemental Table 6). Absolute systolic BP was higher, and diastolic BP remained relatively stable, whereas systolic and diastolic BP z scores were lower over time (Supplemental Figures 4 and 5).

In the model for PWVz and follow-up censored to age ≤17 years (median follow-up 1.25 [IQR, 0–3.8] years), PWVz similarly showed a nonlinear association with time. Other variables that showed significant associations were younger age, girls, lower height z score, higher diastolic BP z score, higher serum LDL cholesterol, higher log UACR, and lower log ferritin. In addition, time interaction analysis revealed an intensifying positive effect of girls over time (Supplemental Table 7).

In both (baseline and longitudinal) models for absolute PWV, mean arterial pressure showed the best model fit (lowest Akaike information criterion) compared with systolic or diastolic BP. Diastolic BP z score was used in the models with PWVz due to better model fit compared with systolic BP z score and inability to standardize calculated mean arterial pressure.

Table 1. Characteristics of study participants at baseline and the number of participants with available data

Characteristic	All Patients, n=667	No. of Patients with Available Data
Age, yr	12±3	667
Boys, *n* (%)	437 (66)	667
Ethnicity, %		667
White	599 (90)	
Non-White	68 (10)	
Small for gestational age, *n* (%)	104 (18)	574
BMI, kg/m^2	18±3	665
BMI *z* score	0.12±1.27	643
Underweight, *n* (%)	54 (8)	643
Overweight, *n* (%)	122 (18)	643
Obese, *n* (%)	34 (5)	643
Height, cm	141±20	667
Height *z* score	−1.26 (−2.08 to −0.45)	667
Short stature, *n* (%)	202 (30)	667
Weight, kg	38±15	667
Pubertal status, *n* (%)		661
Prepubertal	360 (54)	
Pubertal	301 (46)	
Diagnosis, *n* (%)		667
CAKUT	464 (70)	
Glomerulopathies	57 (9)	
CKD post-AKI	35 (5)	
Tubulointerstitial	82 (12)	
Other	29 (4)	
Systolic BP, mm Hg	112±14	667
Systolic BP *z* score	0.83±1.35	667
Diastolic BP, mm Hg	69±12	667
Diastolic BP *z* score	0.69±1.08	667
Mean arterial pressure, mm Hg	84±12	667
Hypertension by office BP, *n* (%)	188 (28)	
eGFR, ml/min per 1.73 m^2	27±12	667
CKD stage 3	245 (37)	
CKD stage 4	319 (48)	
CKD stage 5	103 (15)	
UACR, mg/g	327 (91–1231)	660
Proteinuric, *n* (%)	583 (87)	
Nephrotic-range proteinuria, *n* (%)	88 (13)	
Hemoglobin, g/dl	11.7±1.6	650
Serum bicarbonate, mEq/L	21±4	646
Ferritin, ng/ml	68 (33–142)	610
PTH, pg/ml	125 (71–227)	645
CRP, mg/dl	0.06 (0.02–0.21)	667
Cholesterol, mg/dl	180±51	665
HDL cholesterol, mg/dl	48±14	667
LDL cholesterol, mg/dl	99±40	663
Uric acid, mg/dl	6.5±1.8	665
Serum calcium, mg/dl	9.0±0.7	666
Corrected serum calcium, mg/dl	9.1±0.7	666
Serum phosphate, mg/dl	4.8±1.2	667
Serum albumin, g/dl	3.8±0.6	666
25(OH)-vitamin D3, ng/ml	10.7 (6.3–17.4)	526
PWV, m/s	4.9±0.8	667
PWVz	0.26>2.12	628
PWVz >1.645, *n* (%)	124 (20)	
Antihypertensive medication, *n* (%)	229 (34)	667
ACEi/ARB	170 (23)	
β-blockers	29 (4)	
Calcium channel blockers	64 (10)	
Diuretics	28 (4)	
Other	10 (2)	

Data are presented as mean ± SD, median (interquartile range), or frequency (percentage). BMI, body mass index; CAKUT, congenital anomalies of kidney and urinary tract; UACR, urinary albumin-creatinine ratio; PTH, parathormone; CRP, C-reactive protein; PWV, pulse wave velocity; PWVz, pulse wave velocity standardized to height; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2. Multivariable mixed regression model with random center effect for absolute pulse wave velocity at baseline

Explanatory Variable	Multivariable Regression, Full Model, $n=603$[a]		Multivariable Regression, Stepwise Selection, $n=604$[a]	
	Estimate	95% Confidence Interval	Estimate	95% Confidence Interval
Age, per 1 yr older	0.047	0.01 to 0.08	0.068	0.05 to 0.08
Girls	−0.056	−0.17 to 0.06	−0.061	−0.17 to 0.05
Diagnosis (reference: CAKUT)	0.106	−0.01 to 0.22	—	—
Height, per 1 cm higher	0.004	−0.00 to 0.01	—	—
Mean arterial pressure, per 1 mm Hg higher[b]	0.024	0.02 to 0.03	0.024	0.02 to 0.03
HDL cholesterol, per 1 mg/dl higher	−0.004	−0.01 to −0.00	−0.004	−0.01 to −0.00
Serum calcium, per 1 mg/dl higher	0.066	−0.01 to 0.14	—	—
Log UACR, per 1 log higher	0.031	0.00 to 0.06	0.025	−0.01 to 0.06
Log ferritin, per 1 log higher	−0.073	−0.12 to −0.02	−0.070	−0.12 to −0.02

The full model contains variables with $P=0.20$ in multivariable variable regression adjusted for sex and variables after stepwise selection. CAKUT, congenital anomalies of kidney and urinary tract; —, variable excluded after stepwise selection; UACR, urinary albumin-creatinine ratio.

[a]25(OH)-vitamin D3 levels were not considered for the model.

[b]The model with mean arterial pressure showed the best model fit by Akaike information criterion compared with systolic and diastolic BP (1251, 1280, and 1257, respectively).

Pulse Wave Velocity and CKD Progression

Of 628 patients, 369 reached the composite end point of CKD progression during a median follow-up of 2.4 (IQR, 0.9–4.6) years. Of those, 67 (18%) patients reached eGFR <10 ml/min per 1.73 m^2, 153 (42%) had 50% loss in eGFR, and 149 (40%) started KRT. Patients were censored due to the end of the study period ($n=43$), loss to follow-up ($n=86$), transition to the adult clinic ($n=55$), patient's wish ($n=28$), death ($n=2$), or other reasons ($n=45$).

Kidney survival did not differ when stratifying study cohort by PWVz tertiles at baseline (Figure 3). When added to a Cox proportional hazards regression model that included known predictors of CKD progression, PWVz was not associated with the risk of CKD progression as a baseline or time-varying variable (Table 3).

Discussion

Increased vascular stiffness is a strong predictor of cardiovascular events and all-cause mortality in the general population (19) and in adult patients with CKD (20). We have evaluated the evolution of PWV in a longitudinal manner in the largest study to date, which allows for the estimation of the effects of extended exposure to individual risk factors. Our results confirm that PWV is increased in one fifth of children with CKD and relates to individual components of CKD sequelae but not eGFR *per se*. Finally, we have demonstrated that in contrast to the adult data, PWV in children is not associated with CKD progression.

Studies in adults with predialysis CKD have consistently reported increased arterial stiffness that associates with the decline in kidney function (21). Adults, however, frequently exhibit vascular changes due to long-standing and aging-related comorbidities (*e.g.*, diabetes, smoking, and concomitant chronic diseases). Hence, children are particularly suitable to study the mechanisms and risk factors of vascular injury resulting from CKD in the absence of these confounders. A number of smaller-scale studies have reported increased PWV in children with CKD (6), but no differences were observed in others (7,8). The latter two studies, however, enrolled children with an average eGFR twice as large (~60 ml/min per 1.73 m^2) compared with our cohort. Thus, the effects of potential vascular risk factors would be expected to be much less pronounced compared with advanced CKD.

In accordance to previous findings in the pediatric population (8,22–25), PWV in our study did not relate to eGFR and its change over time. Absolute PWV showed a gradual increase that may mirror physiologic stiffening of the arterial tree as seen in healthy children (11), whereas standardized PWV remained relatively stable during long-term observation. This suggests that other CKD-related vascular risk factors rather than the trajectory of eGFR are related to accelerated arterial stiffening in children. On the other hand, a significant proportion of participants received antihypertensive medications that may exhibit differential effects on PWV. Given that both standardized systolic and diastolic BP values slightly decreased over time (a possible Hawthorne effect), reduced distending pressure could have blunted the trajectory of PWVz. Similarly, the awareness of cardiovascular burden could have had an effect on the overall CKD management of study participants.

Studies involving children with primary hypertension or CKD have reported a close association between PWV and BP (8,26,27). In addition, an analysis of ambulatory BP monitoring data from the 4C study linked higher PWV to different ambulatory BP patterns (26). In line with these findings, we found a consistent effect of BP on higher arterial stiffness, with the strongest effect of mean arterial pressure followed by diastolic BP, which has been also noted in other studies of young adults and children after kidney transplantation (28). The effect of mean arterial pressure could also be explained by its representation of distending arterial pressure, which is a known determinant of arterial elastic properties *via* stress-strain relationships (29). This is supported by studies showing a direct hemodynamic effect of mean arterial pressure on arterial stiffening (30,31). Disentangling the

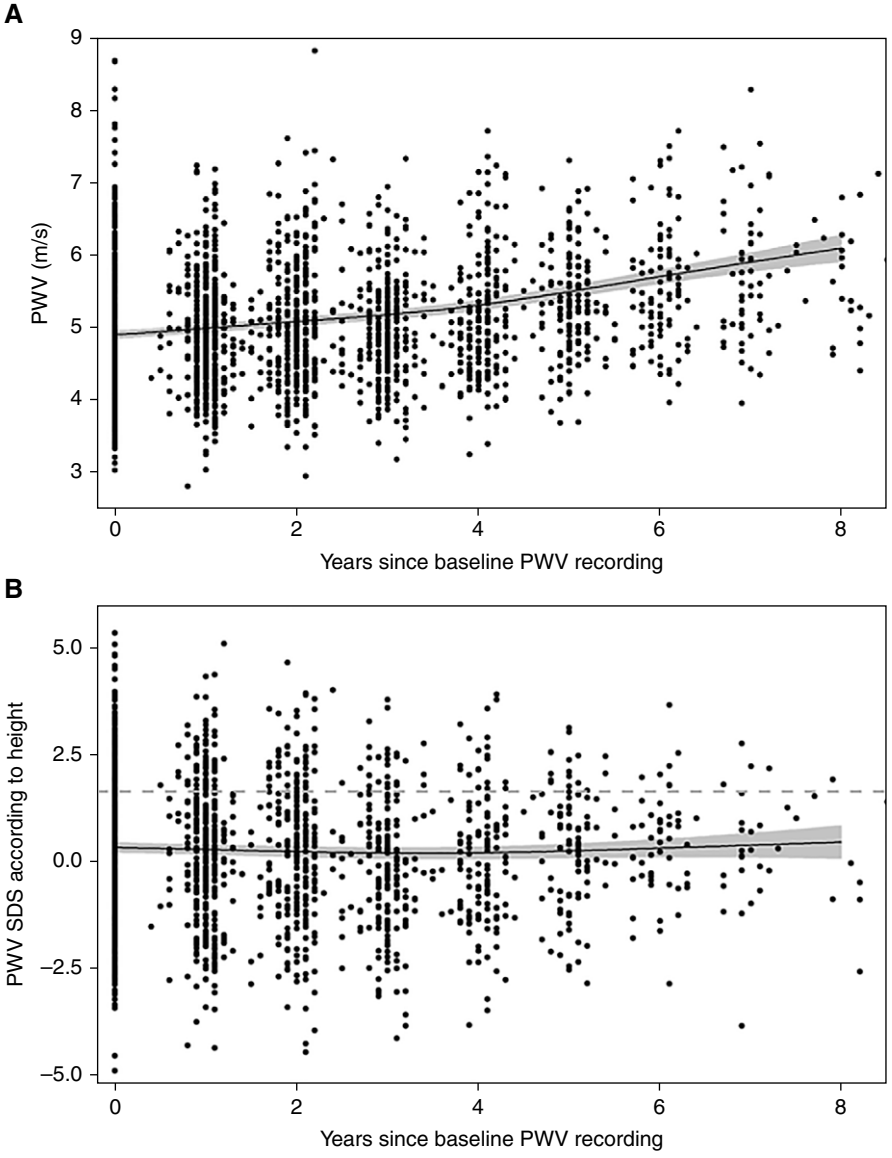

Figure 2. | **Scatterplots showing increasing absolute PWV and relatively stable PWV standardized to height over time during the observation period.** Black dots show the observed data (A: absolute PWV; B: PWV standardized to height), lines show the predicted mean trajectory, and gray areas represent 95% confidence intervals. SDS, standard deviation score (z score).

effects of distending pressure from BP-induced arterial injury is, however, difficult without an in-depth hemodynamic characterization.

We also found a positive association of PWV with proteinuria that may likely be bidirectional; proteinuria might reflect the prevailing generalized vascular disease but may also be a risk factor for cardiovascular disease itself (32,33). However, the effect of proteinuria was observed in the longitudinal analysis only and was attenuated in the multivariable analysis at baseline after adjustment for vitamin D levels (data not shown). Lower vitamin D levels are known to be affected by proteinuria, particularly that of nephrotic range (34). However, because vitamin D levels were available at baseline only, it remains unclear whether the association with proteinuria would persist in longitudinal analysis if vitamin D levels were included. Vitamin D deficiency on its own has been linked to higher risk of cardiovascular disease, increased arterial stiffness, and endothelial dysfunction in adults (35,36), although benefits of vitamin D administration on these outcomes have not been shown in interventional studies.

We have also identified an independent association between lower serum ferritin levels and higher PWV. Studies investigating PWV in adults with and without CKD have reported associations with ferritin that were in the opposite direction of our findings (37–39). These associations are explained by the potential effects of iron overload or by the proinflammatory state reflected by ferritin. The counterintuitive findings of our analysis, however, could be explained by the theoretical protective effects of ferritin on vascular smooth muscle cells (40). A previous *in vitro* study has shown inhibition of

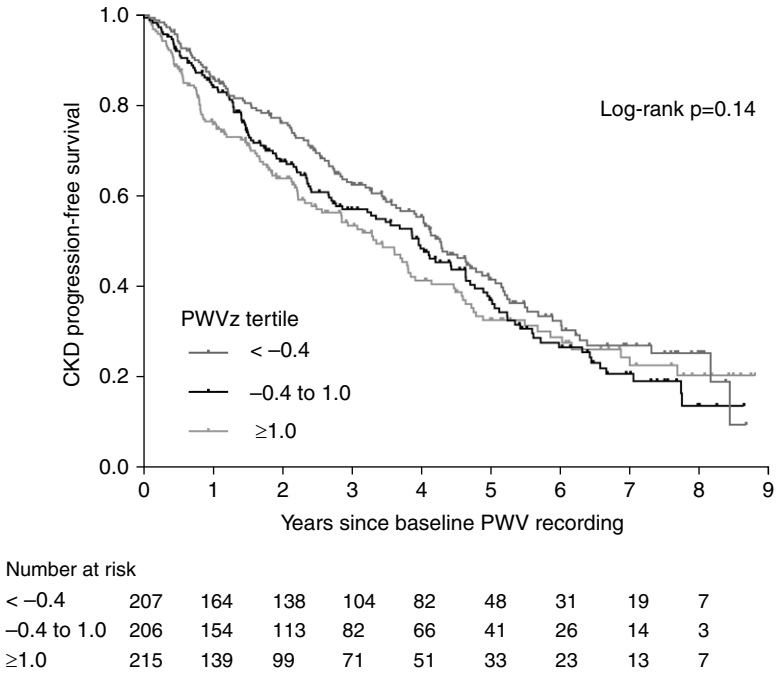

Figure 3. | **Kaplan–Meier curves showing no difference of CKD progression-free survival by PWV standardized to height (PWVz) tertiles.**

calcification and osteoblastic transformation in a culture of human smooth muscle cells after the addition of ferritin (41).

In addition, LDL cholesterol associated with higher PWV over time but not at baseline, suggesting that long-term exposure to increased LDL may contribute to arterial stiffening. These associations could be explained by different mechanisms (premature atherosclerosis, systemic and local inflammation, and effects on endothelial functions) and are supported by studies in hypercholesterolemic children (42).

Arterial stiffness in patients with CKD may result in exacerbation of glomerular hypertension that could contribute to accelerated kidney function decline (43). Although several adult studies reported an independent predictive value of PWV for CKD progression (4,5,44), this association has not been demonstrated in others (45–47). We did not find an association between PWV and CKD progression in our cohort. It may be speculated that the magnitude of PWV increase and exposure duration in childhood is too small to cause substantial kidney damage as compared with adult populations.

In the analysis of standardized PWV, however, we additionally identified several potential nonmodifiable factors associated with higher PWV. Younger children had higher standardized PWV, compatible with the notion that vascular injury in younger age may associate with a worse vascular

Table 3. Cox proportional hazards regression model for the risk of CKD progression including participants with age ≤17 years at baseline and pulse wave velocity standardized for height (n=601)

Explanatory Variable	Model with Baseline Variables		Model with Time-Varying Variables[a]	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Girls	0.90	0.71 to 1.14	0.93	0.74 to 1.18
Age, per 1 yr older	1.04	1.01 to 1.08	1.05	1.02 to 1.09
Diagnosis (reference: CAKUT)				
Glomerulopathies	1.61	1.06 to 2.43	1.72	1.16 to 2.56
CKD post-AKI	1.69	1.06 to 2.71	1.49	0.93 to 2.39
Other	1.40	0.81 to 2.42	1.55	0.92 to 2.61
Tubulointerstitial	1.94	1.42 to 2.66	1.97	1.44 to 2.69
BMI, per 1 z score higher	1.01	0.93 to 1.11	0.97	0.89 to 1.06
Mean arterial pressure, per 1 mm Hg higher	1.01	1.003 to 1.01	1.01	1.005 to 1.02
eGFR, per 1 ml/min per 1.73 m^2 higher	0.92	0.91 to 0.94	0.93	0.92 to 0.94
Log UACR, per 1 log higher	1.47	1.35 to 1.59	1.60	1.46 to 1.74
PWV, per 1 z score higher	0.97	0.90 to 1.04	1.02	0.94 to 1.10

CAKUT, congenital anomalies of kidney and urinary tract; BMI, body mass index; UACR, urinary albumin-creatinine ratio; PWV, pulse wave velocity.
[a]The model incorporated time-varying PWV z score, BMI z score, systolic BP z score, and log UACR.

phenotype. We also found that shorter height for age associates with higher PWV. The mechanistic explanation behind this relationship is unclear, but short stature may mirror the cumulative effect of CKD severity and duration. The association of higher PWV with girls with intensifying effect over time indicates that girls lose the biologically determined favorable vascular profile observed in healthy children with increasing age. Our finding is also remarkable in the context of epidemiologic data indicating worse survival of girls with CKD stage 5 compared with boys (48), and recent data from the 4C study showed greater susceptibility to arterial stiffening in girls before and after kidney transplantation (28). Considering the lack of a standardized approach to analyze PWV values in children and the risks of statistical confounding after standardization, these findings should be interpreted with caution.

Our analysis is subject to several limitations. First, the lack of a prospective control cohort remains a major shortcoming and makes it difficult to tease out the effect of age and growth. Transition to adulthood poses difficulties due to the lack of continuous reference data thereafter. We have sought to address this by performing exploratory analyses and using both absolute and standardized PWV values. In addition, different follow-up times and censoring at KRT may increase the risk of attrition bias and informative censoring. Not all potential risk factors were measured longitudinally. Further, as this is a life course observational study, we are unable to understand the association of treatments (*e.g.*, antihypertensive therapy) with the observed association of CKD and arterial lesions. Finally, the awareness of cardiovascular burden in the study participants may have influenced their management over time, potentially leading to attenuation of arterial stiffening. On the other hand, our analysis is strengthened by the use of longitudinal linear mixed models with patient-individual slopes, which allow for the efficient use of all data and address interindividual variances (49).

In summary, we have shown increased PWV in approximately one fifth of children with advanced CKD that is not related to kidney function changes over time. The identification of modifiable risk factors, such as higher diastolic BP, lower vitamin D levels, proteinuria, and higher LDL cholesterol, suggests added benefits of their control in childhood CKD and prompts further evaluation of PWV in interventional studies. The potential protective properties of ferritin to the arterial tree necessitate additional clinical and mechanistic studies. Although PWV does not associate with the risk of CKD progression in childhood, further studies investigating the effects of early arterial stiffening on cardiovascular outcomes are needed.

Disclosures

A. Duzova reports serving as a council member of International Pediatric Nephrology Association. M. Litwin reports consultancy agreements with Alnylam, Bayer, and Travere and an advisory or leadership role for Bayer. F. Schaefer reports consultancy agreements with Akebia, Alexion, Alnylam, Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Fresenius Medical Care, GSK, Otsuka, Purespring, Relypsa, and Roche; research funding from Fresenius Medical Care; honoraria from Amgen, Kyowa Kirin, Otsuka, and Roche; textbook royalties from Springer; and scientific advisory board activities for Alexion and Otsuka. R. Shroff reports consultancy agreements with AstraZeneca, research funding from Fresenius Medical Care, honoraria from Amgen and Fresenius Medical Care, and speakers bureau for Amgen and Fresenius Medical Care. All remaining authors have nothing to disclose.

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Author Contributions

K. Azukaitis and F. Schaefer conceptualized the study; K. Azukaitis, A. Bayazit, N. Canpolat, A. Doyon, A. Duzova, A. Jankauskiene, A. Melk, M. Litwin, U. Querfeld, F. Schaefer, and R. Shroff were responsible for data curation; K. Azukaitis was responsible for investigation; K. Azukaitis and M. Kirchner were responsible for formal analysis; K. Azukaitis, M. Kirchner, and F. Schaefer were responsible for methodology; K. Azukaitis and M. Kirchner were responsible for visualization; U. Querfeld and F. Schaefer provided supervision; K. Azukaitis wrote the original draft; and A. Bayazit, N. Canpolat, A. Doyon, A. Duzova, A. Jankauskiene, M. Kirchner, A. Melk, M. Litwin, U. Querfeld, F. Schaefer, and R. Shroff reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.02200222/-/DCSupplemental.

Supplemental Material. Supplemental methods.

Supplemental Summary 1. Collaborator information.

Supplemental Table 1. Classification of primary kidney diseases.

Supplemental Table 2. Univariable (pairwise deletion of missing values) and multivariable regression [mixed model with random center effect restricted to the subgroup of patients with available 25(OH)-vitamin D3, full model including all candidate variables with $P=0.20$] with absolute PWV at baseline as the dependent variable.

Supplemental Table 3. Multivariable mixed regression model with random center effect including variables after stepwise variable selection [with log 25(OH)-vitamin D3 levels included among candidate variables] with absolute PWV at baseline as the dependent variable ($n=483$).

Supplemental Table 4. Univariable (pairwise deletion of missing values) and multivariable regression [mixed model with random center effect restricted to the subgroup of patients with available 25(OH)-vitamin D3, full model including all candidate variables] with PWVz at baseline as the dependent variable restricted to patients with age ≤17 years at baseline.

Supplemental Table 5. Multivariable mixed regression model with random center effect including variables after stepwise variable selection [with log 25(OH)-vitamin D3 levels included among candidate variables; $n=462$] with PWVz at baseline as the dependent variable restricted to subjects with age ≤17 years at baseline.

Supplemental Table 6. Associations of time-dependent explanatory variables with absolute PWV over time ($n=2295$ observations from 667 individuals).

Supplemental Table 7. Associations of time-dependent explanatory variables with PWVz over time ($n=1813$ observations from 628 individuals).

Supplemental Figure 1. Distribution of the number of observations per patient of the overall sample (n=667).

Supplemental Figure 2. The proportions and patterns of missing data at baseline.

Supplemental Figure 3. The proportions and patterns of missing data during follow-up.

Supplemental Figure 4. Change of absolute diastolic BP and systolic BP over time during the observation period.

Supplemental Figure 5. Change of diastolic BP and systolic BP z scores over time during the observation period.

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