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Aortic Dilatation in Children and Young People With ADPKD

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Introduction: Aortic root dilatation is a reported cardiovascular sequela seen in children and young people (CYP) with chronic kidney disease (CKD) but has yet to be described in those with autosomal dominant polycystic kidney disease (ADPKD).

Methods: Single center, cross-sectional study in a dedicated ADPKD clinic. Echocardiograms were evaluated for the presence of dilatation (defined by a z-score ≥2 [≥99th percentile] SDs from the mean) at 4 standardized locations, namely the aortic valve annulus, sinuses of Valsalva (SoV), sinotubular junction (STJ), and the ascending aorta. Measurements were compared with a control group to assess prevalence, severity, and determinants of aortic dilatation.

Results: Ninety-seven children, median age (interquartile range) of 9.3 (6.1, 13.6) years were compared with 19 controls without ADPKD or other CKD. The prevalence of dilatation ranged from 5.2% to 17% in ADPKD, depending on anatomical location with no aortic dilatation identified in the control group. In multivariable regression, aortic root dilatation was significantly associated with cyst burden at the aortic valve annulus and SoV ($\beta = 0.42$ and $\beta = 0.39$, both $P < 0.001$), with age at SoV ($\beta = -0.26$, $P = 0.02$), systolic blood pressure (SBP) z-score at SoV ($\beta = -0.20$, $P = 0.04$) and left ventricular mass index (LVMI) at SoV and STJ ($\beta = 0.24$, $P = 0.02$ and $\beta = 0.25$, $P = 0.03$, respectively) following adjustment for age, sex (male or female), body mass index (BMI) z-score, estimated glomerular filtration rate (eGFR), SBP z-score, and LVMI.

Conclusion: Our data suggests increased prevalence of aortic root and ascending aortic dilatation in CYP with ADPKD compared with controls. Further studies are needed to understand the pathogenesis and its contribution to the high cardiovascular morbidity in ADPKD.

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ADPKD is the most common genetic cause of CKD. It is characterized by the formation of fluid-filled cysts which cause progressive impairment of kidney function, ultimately resulting in 5% to 10% of patients with end-stage kidney disease.[1,2]

There are now a wide variety of non-*PKD1*/*PKD2* genes causative of ADPKD or ADPKD-like phenotypes. ADPKD is genetically heterogenous, with *PKD1* and *PKD2* genes affected most commonly and *GANAB*, *DNAJB11*, *IFT140*, and *ALG9* genes less commonly.[3] Alterations in the *PKD1* or *PKD2* genes, encode the ciliary proteins polycystin 1 and 2, whereas other rarer alterations in genes such as *ALG5*, *ALG9*, *DNAJB11*, *GANAB*, or *IFT140* encode proteins which affect the function of the polycystin proteins.[3] Altered polycystin function results in cyst formation in kidneys[1,4] and also in other organs such as the liver and pancreas. Polycystin is also present in vascular smooth muscle cells, and expression of altered polycystin proteins in these tissues results in aneurysm formation and arterial dissection.[1,2,5,6] Although not clearly understood, it is believed that polycystin signaling pathways are important in the maintenance of vascular integrity.[7,8] Recently Liu *et al.*,[9] highlighted a possible pathophysiological genetic interaction linking diverse pathologies of ADPKD with vascular phenotypes by means of the TGF-β signaling pathway in an animal model.

Aneurysm formation is a well-recognized feature of ADPKD and has been reported involving all vascular

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beds.[1,5,6] Intracranial aneurysms have been the most widely reported association.[10,11] Discrete aortic aneurysms and aortic dissection have been reported in both the abdominal and ascending thoracic aorta in individuals with ADPKD with a higher prevalence than the background non-ADPKD population,[12] and in some instances affecting young individuals with ADPKD.[9,13,14]

Bouleti et al.,[15] reported a higher prevalence of aortic root dilatation at the SoV (defined by a z-score >2 SDs) in middle-aged adults with ADPKD than in age-matched controls. Aortic root and ascending aortic dilatation has been reported in childhood CKD,[16,17] including those on hemodialysis[18] with higher risks associated in those with poor nutrition and hypertension.[16] To our knowledge, aortic dilatation has not been systematically evaluated in CYP with ADPKD. Our study objectives in this report were 2-fold as follows: (i) to assess the prevalence and severity of aortic dilatation by echocardiography and (ii) to evaluate the risk associations for increasing aortic dilatation in relation to kidney function and blood pressure (BP) in CYP with ADPKD and to compare these findings with healthy controls.

METHODS

This is a retrospective, single center, cross-sectional report including CYP referred consecutively and seen in a dedicated pediatric ADPKD referral clinic. ADPKD was diagnosed clinically if the child had evidence of kidney cyst/s on renal ultrasound within the context of parental family history of ADPKD, if the child had polycystic kidney involvement in the absence of family history or if ADPKD was confirmed following genetic testing. We included all individuals with ADPKD referred consecutively to the clinic. We excluded those older than 18 years and those with any congenital or structural heart disease. We also excluded those on any antihypertensive medication (7 out of an initial total of 111 patients [6.3%]). Comparison to the children with ADPKD was made with a previously reported cohort recruited prospectively from the background population of sex-matched and BMI-matched normotensive control children.[19] Individuals in this control cohort had normal kidney function, with no known renal or cardiac disease and were selected for the current study if they had acceptable aortic root and echocardiographic imaging. Use of echocardiographic data on imaging archive for this study was approved by the local research ethics committee (Research Ethics Committee reference: 09/H0802/116). Individual patient consent for use of this retrospective data was not required by this approval.

BP was measured in triplicate in all children at the time of the clinic visit with 24-hour ambulatory BP monitoring (ABPM) performed in all those with ADPKD aged 5 years and over. We defined hypertension by office BP (≥95th percentile systolic or diastolic) and by 24-hour ABPM (≥95th percentile 24-hour systolic, diastolic, or mean arterial pressure).[20] The eGFR in ml/min per 1.73 m^2 was calculated using the modified Schwartz formula with our previously described correction factor.[21-23]

We stratified cyst burden on the basis of the number of large cysts (>1 cm in each kidney) as reported recently by Massella *et al*.[24] We categorized global cyst burden to be "low-cyst," if the cumulative cyst score including both kidneys was 0 to 2 and "high-cyst" if the cumulative cyst score including both kidneys was ≥3 (Supplementary Methods).

Echocardiographic Assessments

The aortic diameter was measured from the parasternal long axis view using the inner edge to inner edge technique at end-systole following transthoracic echocardiographic study (Figure 1). Aortic dilatation was defined as z-score ≥2 (≥99th percentile) SDs from the mean at least from one of the following 4 locations within the aortic root and ascending aorta: (i) the aortic valve annulus; (ii) the SoV; (iii) the STJ; or (iv) the ascending aorta measured at its widest diameter, at least 2cm above the STJ. The z-scores were calculated using the Lopez Pediatric Heart Network regression equations and the Haycock formula for body surface area calculation.[25] Studies were analyzed by 1 author (AS) who was blinded to the participants BP, kidney function, and other clinical characteristics. All measurements were performed in triplicate, where possible. Interobserver variability test was carried out in 10 randomly selected subjects by measurements repeated by 2 observers (AS and HB) with the coefficient of variation defined as the SD of difference in measures expressed as a percentage of the mean measurement.

We expressed LVMI, (LVM divided by height in meters raised to allometric power of 2.7 [$g/m^{2.7}$]) as a measure that accounts for body size[26,27] and calculated left ventricular mass for height z-scores.[28] Strict quality control processes were applied as per the American Society of Echocardiography recommendations.[25] Additional echocardiographic parameters that were measured include the presence or absence of aortic regurgitation, which was assessed with color and spectral Doppler imaging from the parasternal and apical echocardiographic windows as per current recommendations.[29,30] Left ventricular hypertrophy was

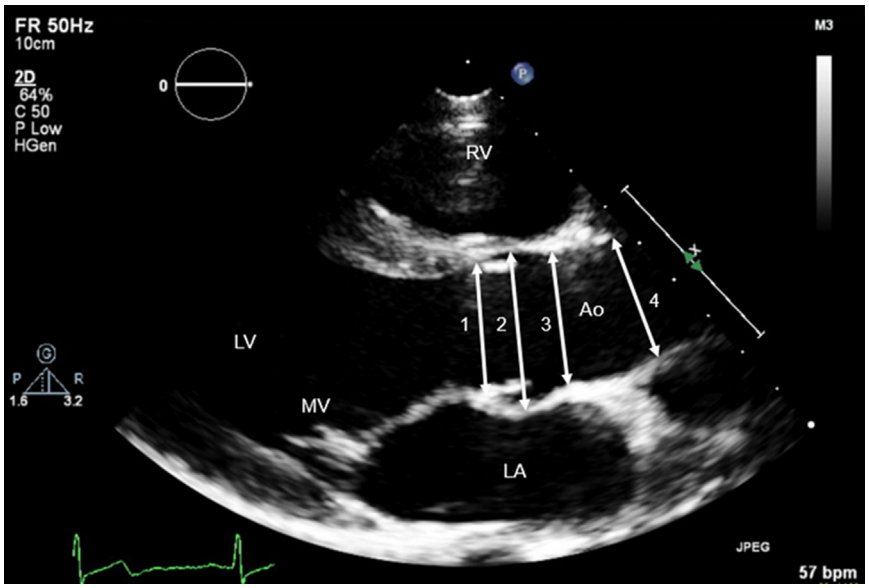

Figure 1. Parasternal long-axis echocardiographic image showing the aortic measurements. Ao, aorta; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle; SoV, sinuses of Valsalva; STJ, sinotubular junction The aortic root and ascending is measured at 4 standardized places, inner-edge to inner-edge technique in end-systole as indicated by the arrows: the aortic valve annulus (1); SoV (2), STJ (3) and the ascending aorta at its widest diameter, at least 2cm above the STJ (4).

defined using age-range specific definition if LVMI >95th percentile by Khoury *et al.*[31]

Statistical Analyses

All data were analyzed using IBM SPSS Statistics for Macintosh, Version 28.0. (IBM Corp, Armonk, NY). All averages were reported as means±SD for normally distributed data and median (interquartile range) for nonnormally distributed data. Differences between categorical variables were assessed using X2 test and between continuous variables using 1-way analysis of variance with Bonferroni post hoc analysis for multiple comparisons. Estimated marginal means were calculated using an analysis of covariance model in which the adjustment variables were inputted as covariates and confidence intervals adjusted for multiple comparisons with Bonferroni correction.

Four separate multiple linear regression models were used to explore the relationship between aortic diameter z-score as a dependent variable (at each of the 4 anatomical locations: aortic valve annulus, SoV, STJ, and ascending aorta) with independent variables including age, sex (male or female), BMI z-score, cyst burden score, SBP z-score, eGFR in ml/min per 1.73 m^2, and LVMI z-score. Multicollinearity was quantified using the variance inflation factor (upper acceptable limit = 4). Goodness-of-fit was expressed as adjusted r^2. Standardized residual plots were inspected for all models and the influence of individual observations were examined using Cooks distance and dfit-beta values with the regression analysis repeated after elimination of all influential outliers. $P < 0.05$ was considered statistically significant and all tests were 2-tailed.

RESULTS

Of 104 CYP aged ≤18 years with ADPKD, we excluded 7 (6.7%) because incomplete data was available, leaving 97 (93.3%) patients in this analysis**.** Table 1 displays demographic and clinical characteristics of those included, with median age (interquartile range) of 9.3 (6.1, 13.6) years, of whom 65% were White Caucasian and 59% were girls. The majority had a low-cyst score following renal ultrasound study ($n = 64$ [66%]) and $n = 7$ (7.2%) had BP in hypertensive range. None of the patients in our study had left ventricular hypertrophy.

Prevalence of Aortic Dilatation

The prevalence of aortic dilatation was 5.2% at the aortic valve annulus, 15.6% at the SoV, 17% at the STJ, and 11.1% at the ascending aorta, with the frequency distribution of aortic dimensions for those with and without ADPKD shown in Figure 2. None of the healthy controls had any aortic dilatation at any of the 4 locations. On interobserver variability analysis, coefficient of variation for aortic diameters was 2.5%, 3.0%, 4.6%, and 6.7% at the aortic valve annulus, the SoV, STJ, and the ascending aorta, respectively.

Severity of ADPKD as Determined by Cyst Burden and Aortic Dilatation

Differences between those with ADPKD and healthy controls, stratified by cyst burden are shown in Table 2. Those in the low-cyst burden group were

Table 1. Demographic and clinical characteristics of 97 children and young people with ADPKD

Clinical characteristics	All ($N = 97$)
Age, yr, median (IQR)	9.3 (6.1, 13.6)
Male sex, *n* (%)	40 (41)
Ethnicity, *n* (%)	
White	63 (65.0)
Black	14 (14.4)
Asian	1 (1.0)
Other	5 (5.2)
Not specified	14 (14.4)
Height, cm, median (IQR)	136.0 (116.5, 160.5)
Weight, kg, median (IQR)	31 (21.5, 51)
BMI, kg/m^2, median (IQR)	17.7 (15.8, 20.5)
Family history of ADPKD	
Paternal inheritance, *n* (%)	35 (36.1)
Maternal inheritance, *n* (%)	55 (56.7)
No known family history, *n* (%)	7 (7.2)
Genetic history	
PKD1 gene alteration, *n* (%)	19 (18.6)
PKD2 gene alteration, *n* (%)	1 (0.9)
Genetic studies not performed, *n* (%)	77 (79.5)
Global cyst burden including both kidneys	
0-2, n (%)	64 (66.0)
3-5, n (%)	21 (21.6)
6-8, n (%)	12 (12.4)
eGFR in ml/min per 1.73 m^2, mean (SD)	95.3 ± 21.4
Prevalence of hypertension	
By office BP, *n* (%)	7 (7.2)
By ambulatory BP ($n = 65$), *n* (%)	4 (6.2)

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range. Data shown as median (IQR) or mean (SD) unless stated.

younger than both controls and high-cyst burden group. Regardless of cyst burden, CYP with ADPKD had a lower eGFR compared to controls, with average eGFR of 95 ml/min per 1.73 m^2 versus 136 ml/min per 1.73 m^2. Higher BP and higher LVMI z-score was recorded in those with high-cyst burden group than in healthy controls. The aortic measurements and their z-scores increased progressively with increasing cyst burden, with the greatest disparity at the 2 proximal aortic locations (the aortic valve annulus and the SoV, Table 2). These differences remained significant despite adjustment for age, sex (male or female), and SBP z-score. There was a stepwise progressive increase in aortic diameter with increasing cyst burden and when cyst burden groups were compared with healthy controls ($P < 0.001$ between groups at all 4 locations) (Figure 3).

Severity of LVMI and Aortic Dilatation

Stratifying patients with ADPKD by tertiles of increasing LVM for height z-score, we observed no clear relationship of increasing LVM for height z-score with BP or renal function; aortic diameter z-scores were comparable across LVM for height z-score tertiles (Supplementary Table S1).

Six children with ADPKD had trivial, central aortic regurgitation. There were no children in the control group with aortic regurgitation.

Determinants of Aortic Root Size in CYP With ADPKD

In multivariable regression, cyst severity maintained the most dominant relationship with aortic root dilatation. Aortic dilatation was significantly associated with cyst burden at the aortic valve annulus and SoV ($\beta = 0.42$ and $\beta = 0.39$, both $P < 0.001$), with age at SoV ($\beta = -0.26$, $P = 0.02$), SBP z-score at SoV ($\beta = -0.20$, $P = 0.04$) and left ventricular mass index at SoV and STJ ($\beta = 0.24$, $P = 0.02$ and $\beta = 0.25$, $P = 0.03$, respectively) following adjustment for age, sex (male or female), BMI z-score, eGFR, SBP z-score, and left ventricular mass index (Table 3). In the subset of patients who underwent ABPM monitoring, there was no difference in findings following inclusion of 24-hour SBP z-score (or other ABPM variables) in multivariable regression analyses. There was no change in findings when evaluating relationships of ABPM at all the aortic sites evaluated here (data not shown). There was no significant interaction between SBP z-scores and cyst score. Aortic dilatation at the ascending aorta location was not explained by any of the evaluated covariates. Variance Inflation Factor in all models was <4.

DISCUSSION

To our knowledge, this is the first report evaluating the prevalence and determinants of aortic dilatation over the first 2 decades of life in patients with ADPKD. Our main findings are that aortic dimensions are increased in those with ADPKD and higher in those with a higher cyst burden, despite relatively good BP and kidney function and when compared with controls who did not have ADPKD.

Our findings are consistent with the report by Bouleti *et al.*,[15] in adults with ADPKD, aged (mean±SD) 56 ± 12 years compared with age-matched controls. They reported a significant increase in the prevalence of aortic dilatation at the SoV location, at 25% in patients with ADPKD versus 7% in controls.[15] Our study adds to their finding by highlighting the childhood onset of these changes in those with ADPKD and identifying the modifiable and nonmodifiable determinants of aortic dilatation. We observed ADPKD disease severity, as represented by cyst burden, had a consistent and dominant association with aortic dimensions, with a lesser influence of BP. This association extended across all the

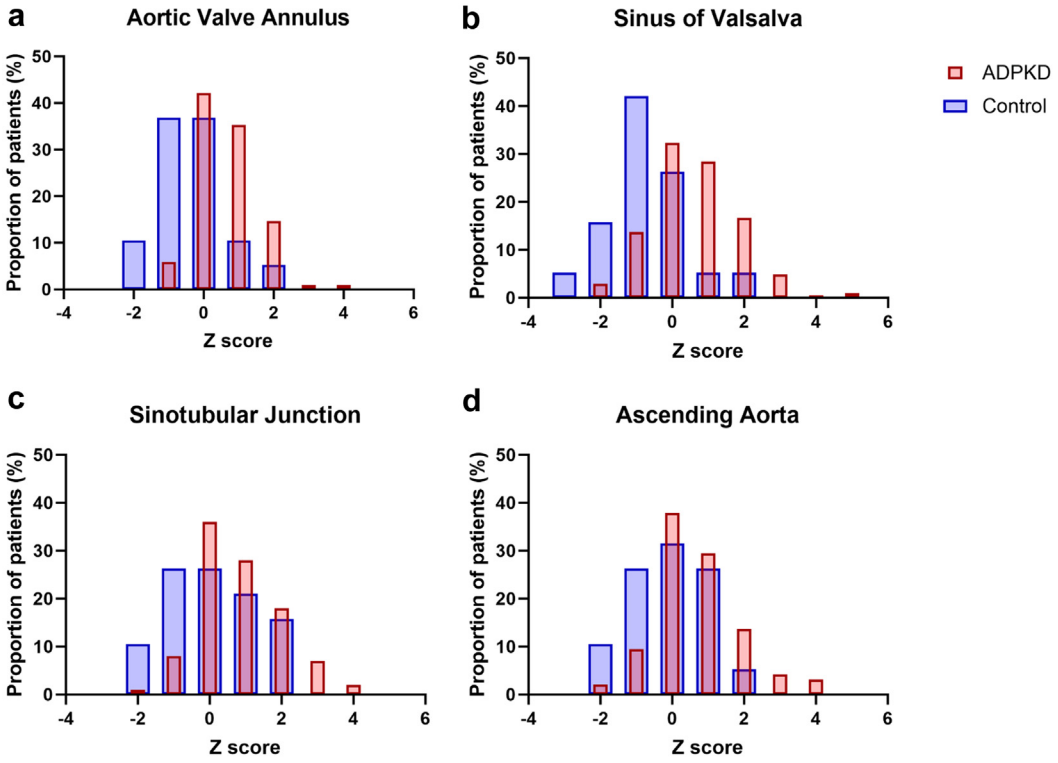

Figure 2. Distribution of aortic z-scores in 97 children and young people with ADPKD and healthy controls without ADPKD. ADPKD, autosomal dominant polycystic kidney disease. Aortic dilatation was defined as z-score ≥2 (≥99th percentile) using the Lopez Pediatric Heart Network regression equations.[23]

aortic measurement sites, most pronounced at the proximal (aortic valve annulus and SoV) locations as compared to the STJ and ascending aorta.

In those with more severe ADPKD phenotype, differences in aortic diameter between cyst burden groups (low-cyst vs. high-cyst), remained significantly higher following adjustment for age, sex (male or female), and SBP. This observation in particular in those with a low-cyst burden suggests that aortic remodeling commences early in ADPKD, alongside the pathological processes leading to cyst formation in the kidney, rather than being primarily driven by structural or functional changes in the kidney.

In those with moderate to severe childhood CKD, aortic dilatation has previously been associated with malnutrition and hypertension.[16,17] We observed aortic dilatation despite well-preserved kidney function and relatively lower BP. The reasons for these differences with our findings are not apparent and may be related to the study population with differing etiologies for CKD, differences in kidney function, and in the duration and severity of hypertension and associated comorbidities. None of the patients in our study had any clinical concern of malnutrition with BMI comparable to control children.

Our data showed a dominant association of cyst burden, with lesser influence of BP with aortic dilatation in this population of childhood ADPKD. We did not though have any patients with severe hypertension, with the few patients with hypertension following evaluation (office or ambulatory) displaying only marginally elevated BP levels. We excluded patients receiving antihypertensive medication to avoid confounding, especially because most children with hypertension and ADPKD are treated with renin-angiotensin-aldosterone system inhibitors, and these medications may modify evaluated findings as a result of their known extrarenal effects. Furthermore, additional details regarding timing, dose, and duration of antihypertensive treatment were not available.

We observed that increasing LVMI had a significant positive association with aortic size, independent of BP in children with ADPKD. Our findings are hypothesis-generating and may reflect a pathophysiological process in those with more severe ADPKD (as represented by higher cyst burden) that is mediated by altered polycystin pathways involving myocytes in the left ventricle and aorta.[32] Further, arterial stiffness, not measured in this study, with or without aortic root dilatation may influence left ventricular structure and function due to altered ventricular ejection hemodynamics as has been shown in individuals with primary hypertension.[33] Studies evaluating these relationships longitudinally in children with ADPKD are indicated.

Table 2. Distribution of blood pressure, anthropometrics, and echocardiographic parameters in 97 children and young people with ADPKD stratified by cyst burden and compared with healthy controls

Characteristics	Controls	Low-cyst 0–2	High-cyst 3 or more	*P*-value
n	19	64	33	n/a
Age, yr (mean±SD)	11.9 ± 4.0	7.7 ± 4.9	12.4 ± 4.2	<0.001[a,c]
Male sex, *n* (%)	5 (26%)	27 (42%)	13 (39%)	0.46
Height, cm, (mean ± SD)	146.9 ± 20.5	123.0 ± 34.2	151.9 ± 23.7	<0.001[a,c]
Height z-score (mean ± SD)	0.044 ± 0.98	0.102 ± 1.43	0.461 ± 1.68	0.46
Weight, kg (mean ± SD)	45.4 ± 20.9	31.0 ± 21.2	46.7 ± 18.1	<0.001[a,c]
Weight z-score (mean ± SD)	0.38 ± 1.15	0.22 ± 1.44	0.22 ± 1.24	0.89
BMI, kg/m^2 (mean ± SD)	19.8 ± 4.6	18.2 ± 4.5	19.3 ± 3.7	0.23
BMI z-score (mean ± SD)	0.48 ± 1.04	0.29 ± 1.29	−0.06 ± 1.77	0.35
eGFR ml/min per 1.73 m^2 (mean ±SD)	135.8± 24.4	98.7 ± 23.5	88.7 ± 15.2	<0.001[a,b]
SBP in mmHg, (mean ± SD)	102.5 ± 12.1	99.1 ± 11.7	110.0 ± 12.4	<0.001[c]
SBP z-score (mean±SD)	−0.167 ± 0.74	0.015 ± 0.83	0.239 ± 0.99	0.24
DBP in mmHg, (mean ± SD)	59.1 ± 10.9	61.7 ± 9.1	66.2 ± 10.7	0.036[b]
DBP z-score (mean±SD)	−0.482 ± 0.90	0.231 ± 0.71	0.275 ± 0.91	0.003[a,b]
MAP, mm Hg, (mean ± SD)	73.6 ± 10.5	74.8 ± 8.8	80.9 ± 9.9	0.007[c]
LVMI, g/m$^{2.7}$, (mean ± SD)	28.0 ± 4.8	34.0 ± 9.9	32.4 ± 9.4	0.047[a]
LVMI z-score (mean±SD)	−1.54 ± 1.01	−1.28 ± 1.02	−0.74 ± 1.13	0.02[b]
AoV diameter, mm (mean±SD)	16.4 ± 2.9	15.3 ± 3.5	19.1 ± 3.0	<0.001[a,b]
AoV Lopez z-score (mean±SD)	−0.353 ± 0.92	0.450 ± 0.76	1.08 ± 0.87	<0.001[a,b,c]
SoV diameter, mm (mean±SD)	22.1 ± 3.4	21.0 ± 4.5	26.6 ± 4.3	<0.001[b,c]
SoV Lopez z-score (mean±SD)	−0.729 ± 1.17	0.377 ± 1.13	1.175 ± 1.22	<0.001[a,b,c]
STJ diameter, mm (mean±SD)	19.2 ± 2.9	17.8 ± 4.4	22.0 ± 3.6	<0.001[c]
STJ Lopez z-score (mean±SD)	−0.071 ± 1.22	0.634 ± 1.25	1.16 ± 0.96	0.002[b]
AsAo diameter, mm (mean±SD)	20.3 ± 3.3	18.6 ± 4.3	23.0 ± 3.8	<0.001[c]
AsAo Lopez z-score (mean±SD)	−0.065 ± 1.16	0.546 ± 1.09	0.968 ± 1.15	0.009[b]

ADPKD, autosomal dominant polycystic kidney disease; AoV, aortic valve annulus; AsAo, ascending aorta; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; MAP, mean arterial pressure; SBP, systolic blood pressure; SoV, sinuses of Valsalva; STJ, sinotubular junction.
[a]Control versus 0–2 group.
[b]Control versus 3 or more group.
[c]0–2 vs 3 or more group.

Renal function was not found to be predictive of aortic diameter. However, our ADPKD cohort had well-preserved eGFR; therefore, this may only be reflective of the early stages of the disease.

The prevalence of central trivial aortic regurgitation may reflect changes in the motion of the aortic valve leaflets and their ability to adequately coapt with increasing aortic root size.[34] This effect may become more significant with further dilatation of the aortic root, causing increasing severity of regurgitation.[35]

Our results suggest there are BP-independent mechanisms involved in vascular changes observed in patients with ADPKD. Morel *et al.*[36] recently demonstrated altered intracellular calcium homeostasis in the aortas of animal disease models (PKD1 +/- knockouts), suggesting our findings may be directly related to expression of abnormal polycystin in the vascular smooth muscle. Further, renin-angiotensin-aldosterone system and sympathetic nervous system activation in the kidney as a result of cyst formation may lead to shear stress in the vessel walls which activates inflammatory cascades and endothelial dysfunction.[37] Systemic endothelial dysfunction and inflammation have both also been observed in early stage normotensive patients with ADPKD[38,39] and may contribute to observed vascular changes. Studies in early stages of ADPKD evaluating large artery hemodynamics, markers of systemic inflammation, and endothelial dysfunction are needed to improve our understanding of the pathophysiology of these observations.

ADPKD is increasingly recognized as a multisystem disease with significant vascular involvement, independent of pathological changes in the kidney.[1] Although it is widely recognized that ADPKD is associated with vascular complications,[5] there are few data regarding hard adverse cardiovascular outcomes and aortic root pathology in patients with ADPKD. Sung *et al.*[12] found increased frequency of a clinically recorded diagnosis of aortic aneurysm and dissection in the health records of Taiwanese adults with ADPKD (0.92%) compared to the general population (0.11%). However, no data regarding the aneurysms, including their size and extent, and risk factors within the ADPKD population were reported.[12] In hypertensive adults, a dilated aortic root is reported to be a risk marker for adverse cardiovascular outcomes

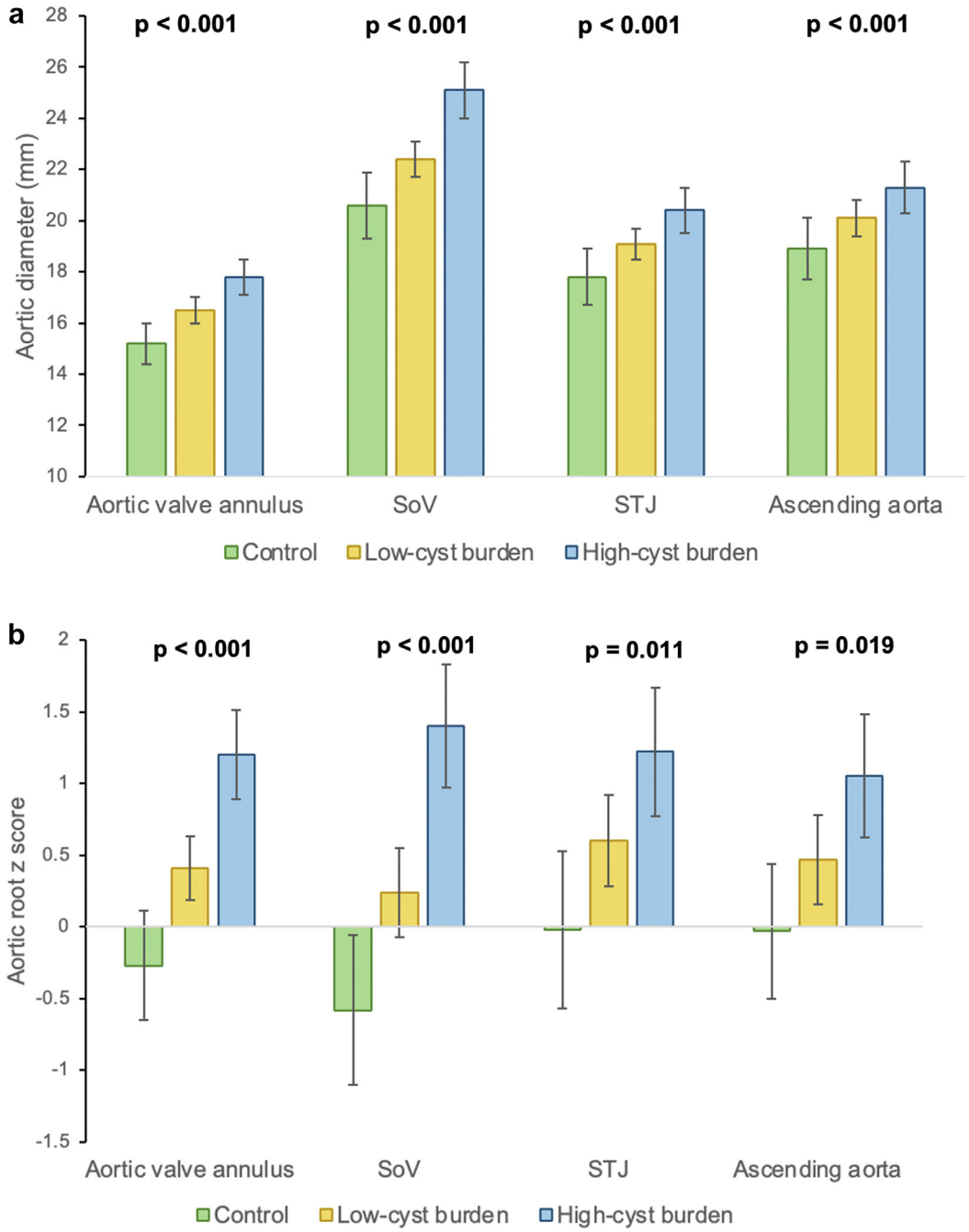

Figure 3. Aortic diameters in mm and as z-scores in 97 children and young people with ADPKD stratified by cyst burden and compared with healthy controls. ADPKD, autosomal dominant polycystic kidney disease; AoV, aortic valve annulus; AsAo, ascending aorta; SBP, systolic blood pressure; SoV, sinuses of Valsalva; STJ, sinotubular junction Data shown as marginal means after adjustment for age, sex (male or female), and SBP z-score. Error bars represent 95% confidence interval. Panel A: aortic diameters in mm; Panel B aortic diameter z-scores. *P*-values refer to difference between groups assessed by analysis of variance.

independent of increased left ventricular mass.[40] It remains important therefore to identify factors and biomarkers that improve our understanding of cardiovascular outcomes in those with ADPKD.

Limitations of our study include those inherent in single-center, retrospective data analysis; although this study includes a relatively large number of patients with ADPKD across the childhood age-range, who had a comprehensive set of investigations performed systematically. We selected the aortic z-score reference data published by Lopez *et al.*[25] to measure the aortic root SD. We accept that there remains a lack of consistency between reported z-score references in the literature.[41] Different sets of z-scores will yield different results, depending upon the population from which they were sampled.[42] The Lopez echocardiographic z-scores from the Pediatric Heart Network Normal Echocardiogram Database from North America

Table 3. Multivariable regression analyses to predict aortic diameter z-scores measured at 4 standardized locations in the aortic root from relevant independent variables

	Aortic valve diameter z-score (Lopez)[a]	Sinus of Valsalva diameter z-score (Lopez)[a]	Sinotubular junction diameter z-score (Lopez)[b]	Ascending aorta diameter z-score (Lopez)[c]
R^2				
Adjusted R^2	0.16	0.18	0.043	0.016
P-value for model	0.002	<0.001	0.151	0.314
Age, Beta coefficient (*P*-value)	−0.17 (0.12)	−0.26 (0.02)	0.04 (0.74)	−0.11 (0.39)
Sex[d], Beta coefficient (*P*-value)	−0.18 (0.08)	−0.10 (0.30)	−0.06 (0.60)	−0.06 (0.57)
BMI z score, Beta coefficient (*P*-value)	0.03 (0.75)	0.01 (0.99)	0.06 (0.60)	0.04 (0.70)
eGFR, Beta coefficient (*P*-value)	−0.03 (0.81)	−0.03 (0.75)	0.04 (0.74)	0.08 (0.52)
Cyst burden[e], Beta coefficient (*P*-value)	0.42 (<0.001)	0.39 (<0.001)	0.16 (0.19)	0.20 (0.11)
SBP z score, Beta coefficient (*P*-value)	−0.18 (0.07)	−0.20 (0.04)	0.04 (0.70)	0.07 (0.57)
LVMI z score, Beta coefficient (*P*-value)	0.12 (0.26)	0.24 (0.02)	0.25 (0.03)	0.16 (0.16)

BMI, body mass index; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; SBP, systolic blood pressure.
[a]$n = 96$.
[b]$n = 94$.
[c]$n = 89$.
[d]Male sex as reference group.
[e]Low cyst burden (0–2) as reference group.
Aortic dilatation was defined as z-score ≥2 (≥99th percentile) using the Lopez Pediatric Heart Network regression equations.[23]

has the largest sample size, $N = 3215$ to date, but may not precisely represent European childhood population.[25] A limitation of the study is the small number of patients in whom genetic testing had been performed. Although this is typical for a cohort of children with a clinical diagnosis of ADPKD in the UK, it restricts our ability to draw conclusions relating genotype to phenotype. Detailed genotyping is necessary for the interpretation of the phenotypic findings described here, and studies considering whether particular genotype predisposes patients with ADPKD to aortic root dilatation are indicated. We included a control group of healthy children for comparison, although we accept that control participants were younger and included limited numbers representing a convenience sample. This may have resulted in an underestimate of the differences in estimates of cardiovascular parameters between groups. A longitudinal study including comparable numbers of CKD and non-CKD non-ADPKD controls is likely to improve our understanding of the relevance of kidney function with aortic dilatation. Finally, ours was a referred population and we accept that our results may not be reflective of the wider childhood ADPKD population. Further longitudinal data are required to improve our understanding of factors impacting on aortic dilatation.

Conclusion

In conclusion, our data suggest increased prevalence of aortic dilatation in CYP with ADPKD. These findings are novel and striking, especially considering that our cohort was naïve to antihypertensive medication, largely normotensive, and had preserved renal function. Further elucidation of the pathogenesis and determinants of progressive aortic root and ascending aortic dilatation in this population may lead to improved clinical outcomes especially in CYP in whom adverse cardiovascular outcomes remain the predominant morbidity.

Clinical Perspectives

Gene defects resulting in ADPKD affect vascular tissue as well as the kidneys, and in adults with ADPKD, both cardiovascular and end-stage kidney disease are the major causes of morbidity and mortality. Our observation of increased prevalence of aortic dilatation in ADPKD and greater dilatation with more severe cyst burden, despite relatively good BP and before the development of significant renal disease is novel and hypothesis-generating. Further studies are needed to understand the pathogenesis of aortic dilatation and its contribution to both renal and cardiovascular morbidity in ADPKD.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental Methods.

Supplemental References.

Table S1. Clinical, demographic, and echocardiographic parameters in 97 children and young people with ADPKD stratified by tertiles of increasing LVM for height z-scores. ADPKD, autosomal dominant polycystic kidney disease; LVM, left ventricular mass.

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