ORIGINAL ARTICLE

Reduced glomerular filtration rate is associated with ascending aortic dilatation in South African chronic kidney disease patients

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ABSTRACT

Background: Ascending aortic dilatation (AAD) is an adverse prognostic cardiovascular marker in the general population. There are few data reporting its presence or clinical significance in chronic kidney disease (CKD) patients. The aim of this study was to evaluate ascending aorta dimensions and their correlates in a population of South African CKD patients.

Methods: A total of 124 CKD patients and 40 healthy controls were enrolled. Cardiac dimensions, systolic and diastolic function indices, and aortic root diameters were assessed by transthoracic echocardiography. The ascending aorta was measured at four levels (aortic annulus, sinuses of Valsalva, sino-tubular junction, and ascending aorta) and was normalised for body surface area. The prevalence of AAD was assessed in CKD patients compared with the control group.

Results: In CKD patients, the ascending aorta dimension was significantly larger than in controls at all four sites of the aorta that were measured. The prevalence of AAD was 6.5% at the annulus, 12.9% at the sinuses, 15.3% at the sino-tubular junction, and 8.9% at the ascending aorta. Overall, 29 patients (23%) had AAD. On multivariate analyses, eGFR was independently associated with AAD (odds ratio 0.980; 95% confidence interval 0.965–0.996; P = 0.014).

Conclusion: AAD is a common cardiovascular phenotype in South African CKD patients. Low eGFR was independently associated with AAD, suggesting a direct link between CKD and the development of AAD in South African CKD patients.

Keywords: chronic kidney disease; cardiovascular disease; ascending aortic dilatation.

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death in patients with chronic kidney disease (CKD), especially in those with end-stage kidney disease (ESKD) [1,2]. CKD is associated with an exceptionally severe cardiovascular risk profile, manifesting with a high incidence of coronary artery disease, sudden cardiac death and major adverse cardiovascular events. These events may be attributed to the many interactions between oxidative stress, systemic inflammation and endothelial dysfunction, leading to abnormal vascular and cardiac remodelling [3].

Ascending aortic dilatation (AAD), which represents arterial vascular remodelling and defined as pathological dilatation of the aortic root, is a predictor of heart failure, stroke, cardiovascular mortality, all-cause mortality, and other devastating cardiovascular outcomes, including aneurysm formation, aortic dissection and rupture [4,5].

Even though it has been widely acknowledged that CKD is a predisposing condition for enhanced cardiovascular risk, reports of the link between estimated glomerular filtration rate (eGFR) and ascending aorta dimension have not been consistent [6-8].

Differences resulting from a lack of a uniform method of measurement of ascending aorta diameter as well as in the definition of AAD [9-13] and heterogeneity of study populations may have contributed to the dissimilar findings in previous studies. Further, there are no existing data on the prevalence of AAD and its association with reduction in GFR among South African CKD patients. The study reported here evaluated ascending aorta dimensions at the aortic annulus, sinuses of Valsalva, sino-tubular junction, and ascending aorta, and determined the prevalence and associated factors for AAD in a population of South African patients with CKD.

METHODS

Study population, anthropometric and clinical data

We enrolled 124 CKD patients (comprising 41 peritoneal dialysis, 41 haemodialysis and 42 stage 3 CKD patients). Forty age- and gender-matched apparently healthy subjects, who were staff and students of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), were recruited to serve as controls. Inclusion criteria were age 18–60 years, receipt of haemodialysis (HD) and peritoneal dialysis (PD) for at least three months at the dialysis unit or attending the renal clinic for at least three months with stage 3 CKD (defined as an eGFR of 30–59 mL/min/1.73 m^2, present for at least three months). The eGFR was calculated from the serum creatinine using the CKD-Epidemiology Collaboration equation (CKD-EPI) formula, without the African American ethnicity factor. Patients were excluded if they had a history of moderate to severe valvular heart disease, congenital or structural heart disease (such as bicuspid aortic valve and cardiomyopathy), atrial fibrillation, diabetes mellitus, previous open-heart surgery or aortic root replacement surgery, or a disorder known to be associated with aortic diseases, including Marfan's syndrome [14].

Information regarding demographic data and tobacco use were documented. Race was self-reported by study participants. Height and weight were measured using the Seca 220 telescopic measuring rod (Seca GmbH, Germany) and body mass index (BMI) was calculated as the ratio of weight (in kg) to height (in metres) squared. Blood pressure was measured non-invasively using a GE Dinamap® DPC121X-IA automated blood pressure monitor (GE Medical Systems Information Technologies, Inc, Milwaukee,

WI, USA). Blood pressure (BP) for HD patients was recorded non-invasively in the arm without the A-V fistula in the sitting position. BP was estimated by averaging all pre-dialysis and post-dialysis BP recordings taken during the month before the study (three measurements per week for a total of 12 measurements). Among PD and CKD patients, BP was recorded at the time of the clinic visit. The BP average of four clinic visits was taken as the patient's actual BP. In the controls, BP was taken in the sitting position after resting for five minutes. The average of three readings taken five minutes apart was then recorded.

Blood sample collection and laboratory analysis

Venous blood was collected in heparinised tubes and tubes containing ethylenediaminetetraacetic acid (EDTA) after a 12-hour overnight fast. Samples for measurements of haemoglobin concentration, creatinine, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides were analysed by the National Health Laboratory Service as part of the routine standard of care using ADVIAR auto-analysers (Siemens Healthcare Diagnostics Inc, USA).

Echocardiography

As previously described [15,16], echocardiography was performed according to the American Society of Echocardiography recommendations using the Philips iE33 machine equipped with a S5-11-5 MHz transducer (Philips Corporation, USA); M-mode, two-dimensional and colour Doppler measurements were recorded. Left ventricular end-diastolic diameter (LVEDD), end-diastolic thickness of the septum and posterior wall were measured in the parasternal long axis view using M-mode, while the linear method and the parasternal long axis approach were used to calculate left ventricular (LV) mass. Left ventricular end-diastolic volume (LVEDV) and left ventricular ejection fraction (LVEF) were measured using the modified Simpson's method from images obtained in the apical 2- and 4-chamber views in end-systole and end-diastole. LV mass was calculated from internal diastolic diameter, posterior wall dimension, and septal dimension. Body surface area (BSA) was calculated by the DuBois formula [17] and was used to index the measurements of LA, LVEDV and LV mass. Mitral inflow velocities during early (E wave) and late (A wave) diastole were recorded at the level of the mitral valve leaflet tips using pulsed-wave Doppler ultrasound. Peak early myocardial diastolic relaxation velocity was measured using tissue Doppler imaging at the base of lateral and septal annulus during early (e' velocity) diastole. Four consecutive cardiac cycles were recorded for off-line analysis and were presented as the mean of the

three consecutive heartbeats. The E/e' ratio was then calculated, and the value was considered to reflect the filling pressures to the LV.

Ascending aorta measurements were obtained in the parasternal long axis view using an inner edge to inner edge technique during systole. Ascending aorta measurements were acquired at the sinus of Valsalva, annulus, sino-tubular junction, and ascending aorta. Ascending aorta dimensions were indexed using body surface area. In adults, it should be noted that ascending aorta dimensions may be influenced by age, sex and height [18]. According to guidelines, normal values for ascending aorta dimensions in adults are: annulus ≤1.4 cm/m^2 (male and female), sinus of Valsalva ≤1.9 cm (male), ≤2.0 cm (female), sinotubular junction ≤1.7 cm (male and female), proximal ascending aorta ≤1.7 cm (male), ≤1.9 cm (female) [19,20]. Upper limits of ascending aorta dimensions were considered to be the mean ± 2 standard deviation (SD) of the values found in normal controls at each level. All measurements were performed by the same echocardiographer, who was blind to the clinical details and laboratory data of the participants.

Data analysis

All data analyses were performed using the statistical package SPSS version 16 (SPSS, Inc., Chicago, IL). Variables were presented as mean ± SD for continuous data, and percentages and frequencies for categorical data. Results were analysed using the t-test and Mann-Whitney U test where appropriate, with the one-way ANOVA tests for comparison across the groups. Correlation between variables was assessed by the Spearman or Pearson correlation coefficients accordingly. A multivariate logistic regression model was created to identify associations of AAD. Factors that are known to be associated with AAD were included in the model: age, gender, mean arterial blood pressure (MABP), and eGFR. A 2-tailed P value less than 0.05 was considered statistically significant. All data were completed, with none missing, for all participants.

ETHICAL CONSIDERATIONS

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Protocol M130127).

RESULTS

Demographics

The study population consisted of 124 CKD patients, whose mean age was 41.2 ± 10.2 (range 20–63) years. Most subjects were male (86, 52%), Black (110, 89%) and had non-glomerular disease (88, 71%); of these 63 (72%)

were hypertensive. Seventeen patients (14%) were active smokers, 29 (23%) reported to have stopped smoking whereas 88 (71%) had never smoked cigarettes. The mean age for the controls was 42.2 ± 10.1 years. Only 2 (5%) of the controls were current smokers. The aetiology of CKD in the 124 subjects was attributed to hypertension in 63 (51%), probable chronic glomerulonephritis 36 (29%), polycystic kidney disease in 8 (7%), reflux nephropathy in 4 (3%), congenital abnormalities of the kidneys in 4 (3%), obstructive uropathy in 3 (2%), and unknown in 6 (5%). These patients had lower eGFR (20.6 vs 100.9 mL/min/1.73 m^2, P < 0.001) and haemoglobin levels (12.4 vs 14.7 g/dL, P < 0.001) than the controls. However, there was no significant difference in lipid levels between the patients and controls. The demographic, clinical and echocardiographic details of the two groups are summarised in Table 1. Only 13 out of 63 (21%) hypertensive patients had AAD.

Prevalence of ascending aorta dilatation and echocardiographic findings

In CKD patients, the ascending aorta diameter was significantly greater than in controls at the annulus, sinuses of Valsalva, sino-tubular junction, and at the level of the ascending aorta (Table 1 and Figure 1). The overall prevalence of AAD in those with CKD, including those on dialysis, was 6.5% at the annulus, 12.9% at the sinuses, 15.3% at the sino-tubular junction and 8.9% at the ascending aorta. Overall, 23% of CKD patients and 15% of healthy controls had AAD (P = 0.260).

Cardiac chamber enlargement was greater among CKD patients compared to the controls (LV mass index: 118.4 ± 40.0 vs 84.4 ± 16.0 g/m^2, P < 0.001; left atrial dimension: 3.9 ± 0.7 cm vs 3.2 ± 0.4 cm, P < 0.001). LVEF was significantly lower in CKD patients than in the controls (58.5 ± 9.0 % vs 65.0 ± 8.1 %, P < 0.001). Patients with CKD had LV diastolic dysfunction, with a significantly lower E/A ratio and higher LV filling pressure (E/e'), than the control group; P < 0.001. However, there was no significant difference in the deceleration time between CKD patients and those with normal kidney function.

Comparison between patients with ascending aortic dilatation and those with normal ascending aorta dimension

Table 2 compares the parameters between patients with AAD and those with normal ascending aorta dimension. Subjects with AAD were anaemic compared with patients with normal ascending aorta dimension (haemoglobin: 10.9 ± 2.7 vs 12.2 ± 2.2 g/dL, P = 0.009) and had severe kidney failure (eGFR: 12.0 ± 4.0 vs 23.3 ± 19.8 mL/min/1.73 m^2, P = 0.005).

Table 1. Demographic, clinical and echocardiographic parameters of study participants.

Parameter	All patients (N=124) mean ± SD	PD (N=41) mean ± SD	HD (N=41) mean ± SD	CKD (N=42) mean ± SD	Control (N=40) mean ± SD	P value*
Age (years)	41.2 ± 10.2	40.6 ± 9.9	40.6 ± 10.1	42.1 ± 10.6	42.2 ± 10.1	0.605
Sex (Male), n (%)	64 (51.6)	22 (53.7)	22 (53.7)	22 (52.4)	22 (55)	0.709
Smoking (Yes), n (%)	17 (13.7)	8 (19.5)	5 (12.2)	4 (9.5)	2 (5)	0.121
Waist: hip ratio	84.1 ± 12.8	82.9 ± 9.4	78.4 ± 11.2	90.3 ± 13.9	83.3 ± 12.3	0.013
Body mass index (kg/m^2)	27.8 ± 6.8	26.3 ± 4.8	25.7 ± 5.1	31.3 ± 7.0	26.6 ± 5.4	0.288
Body surface area (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.7 ± 0.3	1.9 ± 0.2	1.8 ± 0.2	0.925
MABP (mmHg)	108.1 ± 11.3	109.1 ±11.8	110.4 ± 10.6	104.8 ± 11.2	91.9 ± 9.4	<0.001
History of hypertension	63 (50.8)	22 (53.7)	19 (46.3)	22 (52.4)	-	-
Aetiology of CKD						
Non-glomerular	88 (71)	27 (65.9)	31 (75.6)	30 (71.4)	-	-
Glomerular	36 (29)	14 (34.1)	10 (24.4)	12 (28.6)	-	-
eGFR (mL/min/1.73 m^2)	20.6 ± 19.3	-	-	50.8 ± 22.4	100.9 ± 23.9	<0.001
Haemoglobin (g/dL)	11.9 ± 2.4	10.9 ± 2.1	11.1 ± 1.7	11.1 ± 1.7	14.9 ± 1.8	<0.001
Total cholesterol (mmol/L)	4.4 ± 1.3	5.2 ± 1.5	3.4 ± 0.7	4.5 ± 0.9	4.2 ± 1.2	0.519
HDL (mmol/L)	1.3 ± 0.9	1.3 ± 0.4	1.3 ± 1.4	1.3 ± 0.5	1.3 ± 0.4	0.421
LDL (mmol/L)	2.5 ± 1.0	3.1 ± 1.2	1.9 ± 0.6	2.5 ± 0.8	2.3 ± 1.0	0.456
Triglyceride (mmol/L)	1.3 ± 0.8	1.5 ± 0.9	0.9 ± 0.5	1.5 ± 0.7	1.2 ± 0.7	0.172
Left atrium diameter (cm)	4.0 ± 0.7	3.9 ± 0.7	4.2 ± 0.7	3.7 ± 0.6	3.2 ± 0.4	<0.001
Left ventricular end diastolic diameter (cm)	4.7 ± 0.7	4.7 ± 0.7	4.8 ± 0.7	4.6 ± 0.6	4.4 ± 0.3	0.003
Ejection fraction (%)	58.5 ± 9.0	58.6 ± 7.8	58.4 ± 12.2	57.9 ± 5.5	65.0 ± 8.1	<0.001
Interventricular septal thickness (cm)	1.1 ± 0.4	1.2 ± 0.3	1.1 ± 0.2	1.1 ± 0.5	0.8 ± 0.2	<0.001
E/A ratio	1.2 ± 0.5	1.0 ± 0.4	1.2 ± 0.5	1.2 ± 0.6	1.37 ± 0.4	0.010
E/e'	11.2 ± 5.1	226.2 ± 53.6	219.2 ± 64.4	277.0 ± 48.8	6.2 ± 1.7	<0.001
Deceleration time (ms)	224.2 ± 55.6	11.6 ± 5.5	12.9 ± 5.1	12.9 ± 26.1	209.7 ± 34.0	0.051
LVMI (g/m^2)	118.4 ± 40.0	126.9 ± 37.6	120.4 ± 36.8	110.4 ± 41.9	84.4 ± 15.9	<0.001
Aortic annulus (cm/m^2)	1.1 ± 0.2	1.2 ± 0.1	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.1	0.009
Sinuses of Valsalva (cm/m^2)	1.7 ± 0.2	1.8 ± 0.2	1.7 ± 0.8	1.6 ± 0.2	1.6 ± 0.2	0.012
Sino-tubular junction (cm/m^2)	1.4 ± 0.2	1.5 ± 0.3	1.4 ± 0.2	1.3 ± 0.3	1.3 ± 0.2	<0.001
Proximal ascending aorta (cm/m^2)	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	0.034

Abbreviations: MABP, mean arterial blood pressure; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease, HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVMI, left ventricular mass index. *P values were calculated by comparing all patients with kidney disease (n = 124) to controls (n = 40) using Student's t-test.

Correlations between ascending aorta dimension and demographic, clinical and echocardiographic variables
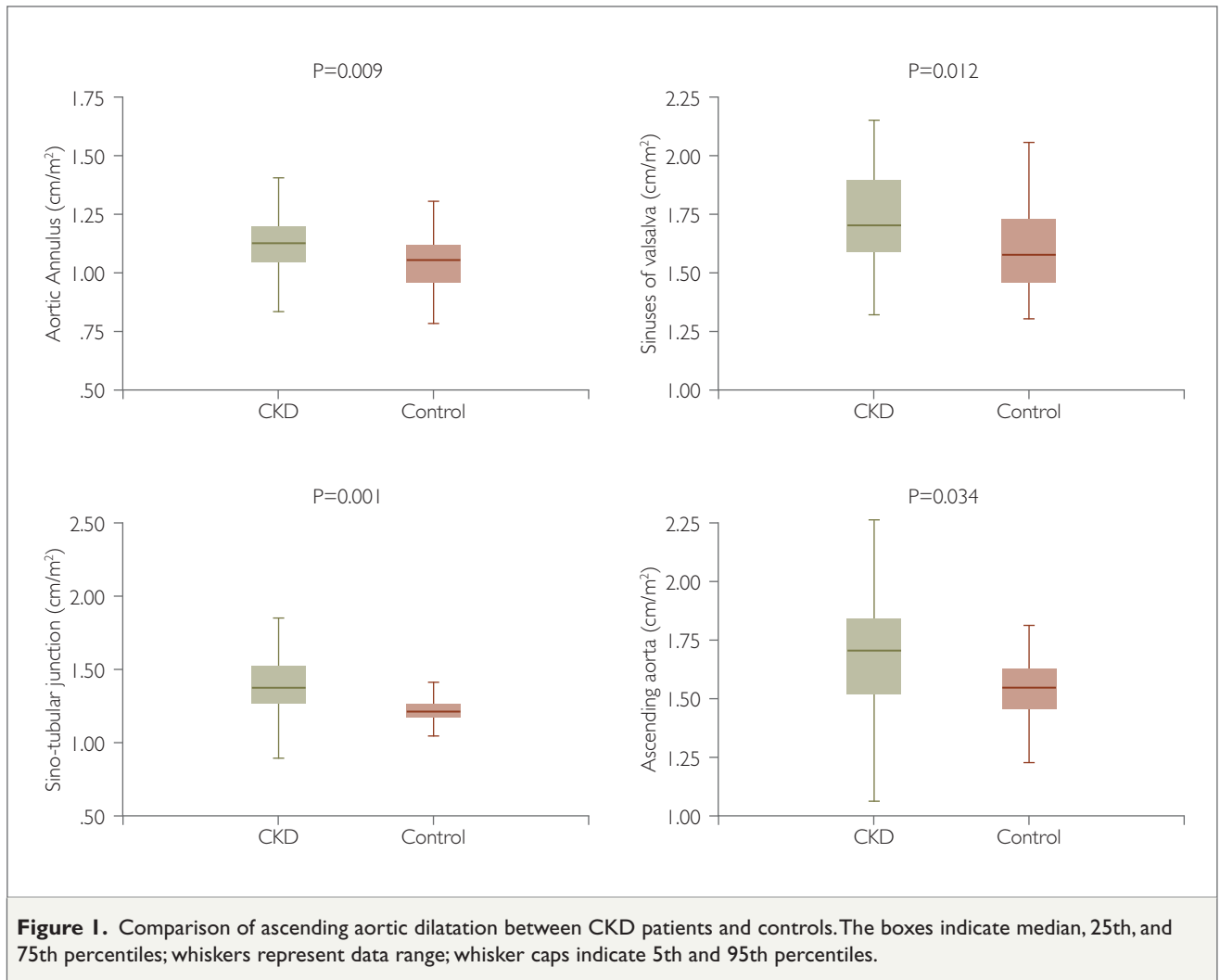
Table 3 shows the correlations between ascending aorta dimensions and demographic, clinical and echocardiographic characteristics of the study population. Mean arterial pressure revealed a weak positive correlation with ascending aorta dimensions whereas eGFR and haemoglobin levels were only slightly negatively correlated.

Multivariate analysis

Multivariable logistic regression analysis demonstrated that eGFR was independently associated with AAD (odds ratio 0.980; 95% confidence interval 0.965–0.996; P = 0.014) (Table 4).

DISCUSSION

This study shows that AAD is common in South African CKD patients, among whom we found an inverse relation-

Figure 1. Comparison of ascending aortic dilatation between CKD patients and controls. The boxes indicate median, 25th, and 75th percentiles; whiskers represent data range; whisker caps indicate 5th and 95th percentiles.

ship between eGFR and ascending aorta diameter corrected for body surface area. Furthermore, after adjustment for multiple confounders, a low eGFR was found to be significantly associated with AAD in our South African CKD patients. This suggests another mechanism for the link between CKD and the increased burden of cardiovascular disease.

Prevalence of ascending aortic dilatation in South African CKD patients

We found a 23% prevalence of AAD in our CKD population. To date, there have been no studies on the ascending aorta size and its associated risk factors in indigenous African CKD populations. Mulé et al. [21], in their study of hypertensive CKD patients, reported a prevalence of 39% among patients with stage 5 CKD and demonstrated that aortic root size increased with the severity of kidney failure. According to these authors, aortic root dilatation was found in 31% and 18% of the patients when aortic root diameter was indexed for height and normalised to body surface area, respectively.

Relationship between aortic root dilatation and eGFR

We found an association between AAD and low GFR in our CKD patients. Moreover, these patients had a higher prevalence of AAD and a larger ascending aorta diameter than the healthy controls, suggesting that advanced kidney failure may represent a novel mediator of thoracic aortopathy in adult CKD patients. While it remains to be seen whether CKD patients with associated AAD are categorically at risk of thoracic aortic aneurysms, previous studies have reported an association between chronic renal insufficiency and risk of developing abdominal aortic aneurysms [23,24]. Considering this evidence, it can be argued that the harmful effect of impaired kidney function may also be extended to the structure of the aorta. Corroborating the findings of our study, Mulé et al. [21] reported an inverse relationship between GFR and indexed values of aortic root size after adjusting for multiple confounders, thereby highlighting the link between renal insufficiency and increased cardiovascular risk mediated by the effect of AAD. However, Li et al. [8], in their study of 5,538 Chinese hypertensive patients, did not find any

Table 2. Comparison of demographic, clinical and echocardiographic parameters of patients with ascending aortic dilatation and those with normal ascending aorta dimension.

Parameter	Patients with AAD (N=29)	Patients with normal ascending aorta (N=95)	P value*
Age (years)	41.2 ± 10.5	41.2 ± 10.1	0.978
Sex (male), n (%)	15 (51.7)	49 (51.6)	0.989
Smoking (yes), n (%)	8 (27.6)	11 (11.6)	0.036
Waist:hip ratio	0.9 ± 0.1	1.3 ± 0.3	0.576
Body mass index (kg/m^2)	24.1 ± 4.2	28.8 ± 6.4	0.001
Body surface area (m^2)	1.7 ± 0.2	1.8 ± 0.2	0.001
MABP (mmHg)	108.4 ± 11.9	101.9 ± 12.4	0.007
Aetiology of CKD			
Non-glomerular	19 (65.5)	69 (72.6)	0.460
Glomerular	10 (34.5)	26 (27.4)	0.465
eGFR (mL/min/1.73 m^2)	12.0 ± 14.0	23.3 ± 19.8	0.005
Haemoglobin (g/dL)	10.9 ± 2.7	12.2 ± 2.2	0.009
Total cholesterol (mmol/L)	4.6 ± 1.4	4.3 ± 1.3	0.185
HDL (mmol/L)	1.1 ± 0.3	1.4 ± 1.0	0.175
LDL (mmol/L)	2.7 ± 1.0	2.4 ± 1.0	0.135
Triglyceride (mmol/L)	1.4 ± 0.9	1.3 ± 0.7	0.663
Left atrial dimension (cm)	3.8 ± 0.6	3.9 ± 0.7	0.781
Left ventricular end diastolic diameter (cm)	4.7 ± 0.8	4.7 ± 0.7	0.505
Ejection fraction (%)	59.7 ± 7.4	58.1 ± 9.4	0.398
Interventricular septal thickness (cm)	1.2 ± 0.6	1.1 ± 0.3	0.106
E/A ratio	1.0 ± 0.4	1.2 ± 0.5	0.040
E/e' ratio	12.4 ± 0.8	10.8 ± 5.1	0.125
Deceleration time (ms)	222.3 ± 50.0	224.8 ± 56.6	0.832
LVMI (g/m^2)	127.3 ± 42.1	115.7 ± 37.8	0.163
Aortic annulus (cm/m^2)	1.3 ± 0.1	1.1 ± 0.1	<0.001
Sinuses of Valsalva (cm/m^2)	1.9 ± 0.2	1.7 ± 0.2	<0.001
Sino-tubular junction (cm/m^2)	1.6 ± 0.2	1.3 ± 0.2	<0.001
Proximal ascending aorta (cm/m^2)	1.8 ± 0.3	1.6 ± 0.2	<0.001

Abbreviations: AAD, ascending aortic dilatation; MABP, mean arterial blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVMI, left ventricular mass index. *P values were calculated by comparing patients with aortic root dilatation (n = 29) to those with normal aortic dimension (n = 95) using chi-squared and t-tests where appropriate.

association between eGFR and indexed aortic root diameter values. Moreover, both the findings of Mulé et al. [21] and of our study (which are procedurally similar) may suggest a specific direct link between persistently low eGFR and elevated cardiovascular risk represented by AAD. The differences observed between us and by Li et al. [8] underscore the need to highlight possible explanations for the seemingly different conclusions between the two investigations.

For example, unlike in the study by Li et al. [8], where ascending aorta diameter was measured at only the annulus level using two-dimensional echocardiography, we employed a more robust method which was based on ascending aorta measurements at four different levels by M-mode tracings, including sinuses of Valsalva that have been commonly used to determine the clinical significance and prognostic value of ascending aorta size in previous studies [11-13,21]. Second, it has been well documented that determinants of the ascending aorta dimension may

Table 3. Correlations of ascending aorta dimensions and some variables studied.

Parameter	Aortic annulus	Sinuses of Valsalva	Sino-tubular junction	Proximal ascending aorta
Age (years)	0.022	0.068	0.082	0.002
BMI (kg/m^2)	−0.550**	−0.519**	−0.430**	−0.519**
MABP (mmHg)	0.265**	0.193*	0.270**	0.173*
eGFR (mL/min/1.73 m^2)	−0.292**	−0.328**	−0.423**	−0.200**
Haemoglobin (g/dL)	−0.329**	−0.347**	−0.325**	−0.257**
Left atrial size (cm)	0.048	0.148	0.285**	0.228**
LVMI (g/m^2)	0.161*	0.176*	0.302**	0.233**
Ejection fraction (%)	−0.013	−0.017	−0.119	−0.010
E/A ratio	−0.197*	−0.258**	−0.230**	−0.064

Abbreviations: BMI, body mass index; MABP, mean arterial blood pressure; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index. *Significant at P value <0.05, **Significant at P value <0.01. Correlation between ascending aorta dimensions and studied variables was assessed by Pearson correlation coefficient.

Table 4. Univariate and multivariable-adjusted odds ratios of factors associated with ascending aortic dilatation.

	Univariate		Multivariable	
Variable	P value	OR (95% CI)	P value	OR (95% CI)
Age (years)	0.978	1.001 (0.960–1.043)	0.472	1.015 (0.975–1.057)
Sex	0.989	0.994 (0.433–2.285)	0.702	1.171 (0.521–2.631)
MABP (mmHg)	0.008	1.047 (1.012–1.083)	0.309	1.020 (0.982–1.059)
eGFR (mL/min/1.73 m^2)	0.009	0.963 (0.936–0.991)	0.014	0.980 (0.965–0.996)

Abbreviations: eGFR, estimated glomerular filtration rate; MABP, mean arterial blood pressure; OR, odds ratio.

differ if the latter is recorded at different ascending aorta levels [9,10]. Finally, Li et al. [8] estimated the GFR using the original version of the CKD-EPI equation that not only included a two-level variable for race (African American and non-African American) but has also been shown to be less accurate in Asian people [25]. However, in our study, we estimated the GFR using the CKD-EPI formula, without the African American correction factor, as it has been shown previously that the CKD-EPI equation is more accurate in African populations when the African American ethnicity factors are omitted [26]. It is therefore plausible that the aforementioned differences may help provide explanations for the seemingly different conclusions of the present study and those of Li et al. [8].

Pathophysiology of ascending aortic dilatation in CKD

Although a close relationship has been established between AAD and renal impairment [2,21], the mechanism for such association is not known. However, a logical pathophysi-ological explanation can be offered on the basis of the

various contributions from multiple risk factors for aortopathy such as volume overload, chronic anaemia, anorexia, hypertension, and the presence of arteriovenous fistulae, which may coexist in patients with CKD [2]. Furthermore, ESKD patients on maintenance haemodialysis are exposed to significant haemodynamic instability as a result of high pulsating pressure and low resistance to flow from alterations in the intravascular volume and myocar-dial stunning following frequent bouts of myocardial ischaemia [27,28]. It is therefore plausible that these alterations may induce degenerative remodelling of the myocardium and vasculature, including the aorta.

Moreover, AAD represents a maladaptive vascular repair which has been linked to CKD. Elevated serum levels of parathyroid hormone in CKD patients could reflect a more advanced chronic kidney disease mineral bone disorder (CKD-MBD), which is closely associated with cardiovas-cular remodelling in CKD [2,29]. Besides, parathyroid hor-mone also has direct vascular effects. Previous experi-mental work has shown the presence of aortic dilatation in uraemic rat models with vascular calcification and ele-

vated parathyroid hormone levels, and demonstrated that aortic dilatation was ameliorated by modest PTH suppression [30]. Thus, the experimental evidence suggests a role for parathyroid hormone and CKD–MBD in the development of AAD in CKD patients.

Relationship between ascending aorta size and hypertensive target organ damage

Even though our data did not indicate any association between AAD and blood pressure on multivariable analysis, we found that AAD correlated with hypertension and markers of hypertension-related cardiac damage such as LV mass index. Taken together, these findings suggest that perhaps both AAD and hypertensive heart disease are manifestations of kidney impairment in CKD patients.

STRENGTHS AND LIMITATIONS

Our study has notable strengths. In contrast to the previous works, which determined aortic dimension only at the level of annulus and Valsalva's sinuses, we evaluated ascending aorta dimensions at the aortic annulus, sinuses of Valsalva, sino-tubular junction, and ascending aorta as equal reflections of abnormal pathology. We also measured aortic root size using M-mode tracings because available evidence about the clinical significance and prognostic value of aortic root size is mostly based on aortic M-mode measurements. Further, we estimated the GFR by using the CKD-EPI equation, without the African American ethnicity factor, thus providing a more accurate estimate of GFR and significantly improving its performance, particularly in Black individuals. However, there were some limitations which need to be considered in interpreting the results. This study was observational and cross-sectional in design; any cause-and-effect relationship between reduced eGFR levels and AAD remains to be established. Moreover, this was a single-centre study that included a relatively small population of CKD patients; thus, the results may not be generalised to all CKD patients. The ascending aorta measurements were performed using the inner edge to inner edge technique during systole. The 2017 guidelines for standardisation of adult transthoracic echocardiography recommend measuring the aortic annulus in mid-systole, and the other ascending aorta measurements at end-diastole. Also, the guideline recommends measuring from the inner edge to inner edge only for the aortic annulus and the leading edge to leading edge measurement techniques for the other ascending aorta measurements [19]. However, considering the recruitment period of our study (April–December 2013), it was not possible to have the ascending aorta measured according to the new guidelines because, at that time, how to measure the aorta in 2D had not been defined. Moreover, because the study population was predominantly young Blacks, with a relatively low burden of atherosclerotic CVD and non-calcified arterial wall layers, the inner edge to inner edge measurements were easily obtained. On the other hand, left atrial volume is a more accurate marker of left atrial size than left atrial diameter [15], and it has also been shown to be a better predictor of cardiovascular events [31]; however, left atrial diameter is readily recorded and has been used extensively in clinical practice. Larger longitudinal follow-up studies are required to investigate potential effects of kidney function on the occurrence and prognosis of aortopathy in this population. We did not perform CT scanning, cardiac magnetic resonance imaging or three-dimensional echocardiography, which could have helped to validate our results further. Nevertheless, available evidence suggests that the clinical significance and prognostic value of ascending aorta size is commonly based on aortic M-mode measurements using echocardiography [11-13]. At present, CT scanning is used more in measuring the aortic annulus before transcatheter aortic valve implantation (TAVI) and transcatheter aortic valve replacement (TAVR) procedures [20]. The classification of CKD may have been different if cystatin C had been used to calculate eGFR instead of creatinine only. In spite of these drawbacks, we believe that our findings justify a need for additional future prospective studies to screen noninvasively and to carry out detailed evaluation of ascending aorta structure with the sole aim of early recognition in CKD patients with attendant high cardiovascular risk. Moreover, the effect of parathyroid hormone and CKD–MBD was not analysed because of the study design. A long-term observational study is needed to determine levels of parathyroid hormone and other markers of CKD–MBD and their associations with AAD in patients with CKD.

CONCLUSION

This study reports the first data on ascending aorta dimensions and the prevalence of AAD is in South African CKD patients. AAD appears relatively common in this population and eGFR was inversely related to ascending aorta diameter. Persistently low GFR was independently associated with AAD, thus suggesting a direct link between kidney failure and the development of AAD in South African patients with CKD.

Disclosure

The authors declared no conflict of interests.

REFERENCES

1. Daly C. Is early chronic kidney disease an important risk factor for cardiovascular disease? A background paper prepared for the UK Consensus Conference on early chronic kidney disease. Nephrol Dial Transplant. 2007; 22(Suppl.9):19-25.

2. Kaddourah A, Uthup S, Madueme P, O'Rourke M, Hooper DK, Taylor MD, et al. Prevalence and predictors of aortic dilation as a novel cardiovascular complication in children with end-stage renal disease. Clin Nephrol. 2015; 83(5): 262-71.

3. Ravarotto V, Simioni F, Pagnin E, Davis PA, Calò LA. Oxidative stress – chronic kidney disease – cardiovascular disease: A vicious circle. Life Sci. 2018; 210:125-31.

4. Gardin JM, Arnold AM, Polak J, Jackson S, Smith V, Gottdiener J. Usefulness of aortic root dimension in persons > or = 65 years of age in predicting heart failure, stroke, cardiovascular mortality, all-cause mortality and acute myocardial infarction (from the Cardiovascular Health Study). Am J Cardiol. 2006; 97(2):270-5.

5. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Catheter Cardiovasc Interv. 2010; 76(2): E43-86.

6. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular disease in chronic kidney disease: Pathophysiological insights and therapeutic options. Circulation. 2021; 143(11):1157-72.

7. Hassan MO, Oguntola SO, Duarte R, Naicker S. Cardiovascular disease in chronic kidney disease – a review of risk factors. Afr J Nephrol. 2020; 23(1):152-8.

8. Li Z, Guo X, Sun Y. Relationship between aortic root size and glomerular filtration rate in hypertensive patients. J Hypertens. 2016 34(6):1232-3.

9. Milan A, Tosello F, D N, Avenatti E, Leone D, Magnino C, et al. Ascending aortic dilatation, arterial stiffness and cardiac organ damage in essential hypertension. J Hypertens 2013; 31:109–16.

10. Kim M, Roman MJ, Cavallini C, Schwartz JE, Pickering TG, Devereux RB. Effect of hypertension on aortic root size and prevalence of aortic regurgitation. Hypertension. 1996; 28:47-52.

11. Cuspidi C, Meani S, Fusi V, Valerio C, C S, Zanchetti A. Prevalence and correlates of aortic root dilatation in patients with essential hypertension: relationship with cardiac and extra-cardiac organ damage. J Hypertens 2006; 24:573-80.

12. Covella M, Milan A, Totaro S, Cuspidi C, Re A, Rabbia F, et al. Echocardiographic aortic root dilatation in hypertensive patients: a systematic review and meta-analysis. J Hypertens 2014; 32:1928-35.

13. Cuspidi C, Facchetti R, Bombelli M, Re A, Cairoa M, Sala C, et al. Aortic root diameter and risk of cardiovascular events in a general population: data from the PAMELA study. J Hypertens 2014; 32:1879-87.

14. Zanjani KS, Niwa K. Aortic dilatation and aortopathy in congenital heart diseases. J Cardiol. 2013; 61:16-21.

15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(3):233-71.

16. Lang R, Bierig M, Devereux R, Flachskampf F, Foster E, Pellikka P, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18(12):1440-63.

17. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989; 5(5):303-11.

18. Vasan RS, Larson MG, Levy D. Determinants of echocardiographic aortic root size. The Framingham Heart Study. Circulation. 1995; 91(3):734-40.

19. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017; 18(12):1301-10.

20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1):1-39.e14.

21. Mulé G, Nardi E, Morreale M, S DA, Foraci AC, Nardi C, et al. Relationship between aortic root size and glomerular filtration rate in hypertensive patients. J Hypertens. 2016; 34(3):495-504.

22. Obremska M, Boratyńska M, Szymczak M, Zyśko D, Płonek T, Goździk A, et al. Aortic root dilation in kidney transplant recipients. Pol Arch Intern Med. 2018; 128(5):287-93.

23. Iribarren C, Darbinian JA, Go AS, Fireman BH, Lee CD, Grey DP. Traditional and novel risk factors for clinically diagnosed abdominal aortic aneurysm: the Kaiser multiphasic health checkup cohort study. Ann Epidemiol. 2007; 17:669-78.

24. Chun KC, Teng KY, Chavez LA, Van Spyk EN, Samadzadeh KM, Carson Teng KY, et al. Risk factors associated with the diagnosis of abdominal aortic aneurysm in patients screened at a regional Veterans Affairs healthcare system. Ann Vasc Surg. 2014; 28:87-92.

25. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604-612.

26. Bukabau JB, Yayo E, Gnionsahe A, Monnet D, Pottel H, Cavalier E, et al. Performance of creatinine- or cystatin C-based equations to estimate glomerular filtration rate in sub-Saharan African populations. Kidney Int. 2019; 95(5):1181-9.

27. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009; 4(12):1925-31.

28. McIntyre CW, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CSR, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. Clin J Am Soc Nephrol. 2008; 3(1):19-26.

29. Querfeld U, Haffner D. Aortic dilatation in children with chronic kidney disease. Pediatr Nephrol. 2020; 35(10):2011. doi:10.1007/s00467-020-04620-5

30. Jung S, Querfeld U, Muller D, Rudolph B, Peters H, Kramer S. Submaximal suppression of parathyroid hormone ameliorates calcitriol-induced aortic calcification and remodeling and myocardial fibrosis in uremic rats. J Hypertens. 2012; 30:2182-2191.

31. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol. 2006; 47(5):1018-23.