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Diabetes attenuated age-related aortic root dilatation in end-stage renal disease patients receiving peritoneal dialysis

Min Ye[1], Jingwei Zhang[1], Jianbo Li[2,3], Yanqiu Liu[1], Wei He[1], Hong Lin[1], Rui Fan[1], Cuiling Li[1], Wei Li[1], Donghong Liu[1], Fengjuan Yao[1,*]

Departments of [1]Ultrasound, Institute of Diagnostic and Interventional Ultrasound, [2]Nephrology, The First Affiliated Hospital of Sun Yat-sen University, and [3]Key Laboratory of Nephrology, Ministry of Health and Guangdong Province, Guangzhou, China

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***Correspondence**
Fengjuan Yao
Tel.: +86-20-8775-5766-8106
Fax: +86-20-8773-30939
E-mail address:
yaofengjuan@hotmail.com

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ABSTRACT

Aims/Introduction: Recently, some data have supported the concept that diabetes is negatively associated with aortic aneurysm. In the present study, we aimed to investigate the relationship between diabetes and cardiac structural and functional characteristics, in particular, aortic root dimensions, in end-stage renal disease (ESRD) patients.

Methods: ESRD patients receiving peritoneal dialysis for >3 months were consecutively enrolled. Clinical features and echocardiographic parameters were analyzed according to the presence of diabetes history. Correlation analyses were carried out for diabetes mellitus and aortic root dilatation. Multiple logistic regression analysis was carried out to identify variables correlated with aortic root dilatation.

Results: A total of 218 ESRD patients receiving peritoneal dialysis were enrolled. Patients with diabetes showed lower left ventricular internal measurements in end-diastole, left ventricular internal measurements in end-systole and aortic root diameter (ARD)/body surface area (BSA). Worse cardiac diastolic function was also observed in these patients. In addition, the age-related increase of ARD/BSA and ARD/height was attenuated in patients with diabetes. With the increase of ARD/BSA, lower levels of serum creatinine, phosphorus and serum glucose, as well as higher serum high-density lipoprotein cholesterol and apolipoprotein A-1 were also observed. Increased normalized left ventricular internal measurements were shown in patients with greater ARD/BSA. Multiple regression analysis showed that diabetes (odds ratio 0.353, $P = 0.015$) was an independent correlate of aortic root dilatation, even after correction for age, sex and other clinical confounders in the enrolled patients.

Conclusions: The present findings shown an inverse association between diabetes and age-related aortic root dilatation in ESRD patients. Diabetes remained to be independently correlated with aortic root dilatation even after adjustment for age, sex and other clinical confounders in ESRD patients.

INTRODUCTION

It has been widely acknowledged that patients with chronic kidney disease, especially end-stage renal disease (ESRD), suffer from the increasing burden of cardiovascular diseases. A higher incidence of coronary artery disease and sudden death, as well as major adverse cardiovascular events, was observed in this population, which might be partially attributed to their vicious interactions between oxidative stress, inflammatory process and endothelial dysfunction[1]. Results from a meta-analysis that enrolled 105,872 participants from 14 studies showed that reduced estimated glomerular filtration rate and elevated urine albumin-to-creatinine ratio were correlated with higher all-cause mortality[2]. Common echocardiographic findings in ESRD patients include elevated left atrial volume, left ventricular hypertrophy, impaired LV diastolic and systolic function, right ventricular systolic dysfunction, aortic valve calcification, and so on[3].

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In a recent study, an inverse correlation between aortic root dimension and estimated glomerular filtration rate was elucidated[4]. An enlarged aortic root, possibly indicating the occurrence of arterial ventricular remodeling, was associated with an increased risk of heart failure[5]. Furthermore, in the Cardiovascular Health Study, which enrolled 3,933 patients aged >65 years, aortic root dimension was regarded as a potential predictive factor for the incidence of heart failure, stroke, cardiovascular mortality and all-cause mortality[6].

Although diabetes mellitus has long been recognized as a pivotal cardiovascular risk factor, a paradoxical negative correlation between diabetes and the incidence of abdominal aortic aneurysm was shown. Likewise, the growth rate of abdominal aortic aneurysm expansion decreased in these patients[7]. Similarly, in a study by D'Cruz *et al.*[8], which enrolled 1,006,360 patients from five population cohort studies and five case–control studies, the incidence of thoracic aortic aneurysm decreased by approximately 23% in diabetes patients. Recently, Nardi *et al.*[9] showed an inverse correlation between diabetes and normalized aortic root dimension in patients with hypertension, even after adjusting for age, sex and other confounders. In patients with advanced coronary artery disease, lower infrarenal and ascending aortic dimensions were also shown in diabetes patients[10].

Nevertheless, the relationship between aortic root dimension and diabetes in ESRD patients remained unknown. In the present study, we aimed to investigate the relationship between diabetes and cardiac structural and functional characteristics, in particular, aortic root dimension, in ESRD patients.

METHODS

Study population

ESRD patients, receiving peritoneal dialysis for >3 months, were consecutively enrolled in the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China between July 2013 and April 2014. Additional inclusion criteria were: conventional laboratory measurements and echocardiography were carried out. Patients were excluded when there was a history of coronary artery disease, cardiomyopathy, severe valve disease and congenital heart disease. Patients with bicuspid aortic valve, large-vessel vasculitis, Marfan syndrome or Loeys–Dietz syndrome were also excluded.

This study complied with the Declaration of Helsinki, and ethical approval was obtained from the Ethical Review Committee of the First affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from all enrolled participants.

Clinical features

Detailed medical records during hospitalization were collected, including age; sex; body mass index; dialysis duration; combined diseases, such as diabetes and hypertension; blood pressure; and routine laboratory parameters, such as serum creatinine, estimated glomerular filtration rate, hemoglobin, lipid (triglyceride, total cholesterol, high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol), apolipoprotein, uric acid, glucose, calcium, phosphorus, pro-brain natriuretic peptide and so on. Body surface area (BSA) was calculated using the Dubois formula, which was equal to $0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$. Diabetes diagnosis was made according to American Diabetes Association criteria; that is, glycated hemoglobin value ≥6.5%, fasting glucose ≥126 mg/dL (7.0 mmol/L) or 2-h glucose ≥200 mg/dL (11.1 mmol/L), or treated with antihyperglycemic agents[11].

Echocardiography

Echocardiographic evaluation was carried out using a commercial ultrasound imaging system (Vivid 7; GE Health Medical, Milwaukee, WI, USA) with a multifrequency transducer (M3S 1.7/3.4 MHz). All echocardiographic parameters were obtained according to the recommendations of the American Society of Echocardiography[12,13]. The linear left ventricular internal measurements in end-diastole and end-systole were acquired in the parasternal long-axis view at or immediately below the level of the mitral valve leaflet tips with M-mode echocardiography. Left ventricular ejection fraction was calculated from the Teicholz formula. Peak velocities of early filling (*E*), atrial filling (*A*) and the *E*/*A* ratio were recorded in the apical four-chamber view using pulsed wave Doppler. Early lateral mitral annulus velocity (*e*') was recorded in the apical four-chamber view using tissue Doppler imaging with a Nyquist limit of 15 cm/s, then *E*/*e*' ratio was calculated[14].

Aortic root diameter (ARD) was measured at the level of Valsalva's sinuses using M-mode echocardiography, under two-dimensional control, as the maximal distance between the anterior and posterior aortic root walls, then normalized to BSA (ARD/BSA) or height (ARD/H). Aortic root dilatation was defined as ARD/BSA ≥2.2 cm/m^2 in women or 2.1 cm/m^2 in men[15]. Left ventricular mass was calculated using the Cube formula $(0.8 \times 1.04 \times [(\text{IVS} + \text{LVID} + \text{PWT})^3 - \text{LVID}^3] + 0.6)$ (g) and normalized to BSA (left ventricular mass index). Left ventricular hypertrophy was defined as left ventricular mass index >115 g/m^2 in men and >95 g/m^2 in women. Relative wall thickness was equal to (2 × posterior wall thickness) / (LV internal diameter at end diastole).

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation or median (range), whereas categorical variables were described as the frequency and percentage. Conformity to normal distribution was evaluated for continuous variables using both the Kolmogorov–Smirnov and Shapiro–Wilk tests. When comparisons were made in terms of clinical features and echocardiographic parameters among groups, one-way ANOVA test or non–parametric Kruskal–Wallis test was used to make comparisons for continuous variables, whereas the χ^2-test or Fisher's exact test were applied for categorical variables.

Student's *t*-test or non-parametric test for independent samples was carried out to make comparisons on echocardiographic parameters in patients with and without diabetes. Multiple linear regression analysis was executed to investigate the correlation between age and ARD/BSA or ARD/H. Then multivariate logistic regression analysis was carried out to investigate risk factors for aortic root dilatation. A two-tailed *P*-value <0.05 was considered as statistically significant for all analysis executed. Statistical analyses were carried out using SPSS, version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Reproducibility analysis

To assess the interobserver variability, measurements derived from echocardiography were assessed by two independent investigators who were unaware of the other's measurements in 25 randomly selected patients. The results were analyzed using Spearman's correlation test, and the interobserver correlation coefficients were quite high (r = 0.92–0.98, $P < 0.001$). For intra-observer variability, the echocardiographic parameters were tested by the same observer repeated twice, and the results were also well correlated (r = 0.94–0.98, $P < 0.001$).

RESULTS

Clinical features of the enrolled population

A total of 240 ESRD patients fulfilled the inclusion criteria, then 22 were excluded for incomplete laboratory or echocardiographic parameters. Thus, 218 patients with a mean age of 49.5 years were enrolled for further analysis. Men accounted for 50.9% of the entire population. A total of 28.9% of the enrolled population had diabetes mellitus. Among patients with diabetes mellitus, the mean duration of diabetes mellitus was 13.7 ± 7.7 years, and 93.2% received insulin therapy, whereas 6.8% received oral antidiabetic drugs, such as metformin, sulfonylurea, alpha-glucosidase inhibitor or glinide.

As aortic root diameters were normalized to BSA, patients were divided into three groups according to the tertiles of

Table 1 | Clinical features in end-stage renal disease patients grouped by aortic root diameter/body surface area tertiles

Clinical features	Aortic root diameter/BSA tertiles (cm/m^2)			*P*	*P*-trend
	<1.94 (*n* = 70)	1.94–2.12 (*n* = 75)	>2.12 (*n* = 73)		
Men, *n* (%)	37 (52.9)	40 (53.3)	34 (46.6)	0.660	0.450
Age (years)	47.8 ± 14.0	49.3 ± 15.6	50.0 ± 16.6	0.680	0.388
BMI (kg/m^2)	23.7 ± 3.3	22.0 ± 2.6	20.7 ± 2.6	<0.001	<0.001
BSA (m^2)	1.7 ± 0.1	1.6 ± 0.1	1.5 ± 0.1	<0.001	<0.001
Dialysis duration (m)	32.7 ± 23.7	33.8 ± 22.3	32.1 ± 20.9	0.901	0.877
Diabetes, *n* (%)	31 (44.3)	19 (25.3)	13 (17.8)	0.002	0.001
Hypertension, *n* (%)	69 (98.6)	74 (98.7)	71 (97.3)	0.845	0.762
Systolic BP (mmHg)	144.3 ± 21.9	142.6 ± 18.1	139.7 ± 18.2	0.359	0.158
Diastolic BP (mmHg)	85.2 ± 13.1	83.1 ± 12.6	83.7 ± 13.6	0.600	0.489
Creatinine (umol/L)	1095.6 ± 362.2	1015.6 ± 280.1	945.7 ± 268.1	0.015	0.004
eGFR (mL/min)	4.7 ± 4.5	4.5 ± 1.8	4.7 ± 1.6	0.860	0.993
Hemoglobin (g/L)	105.5 ± 19.4	109.4 ± 19.9	108.4 ± 18.3	0.447	0.361
TG (mmol/L)	1.6 ± 1.3	1.6 ± 1.3	1.6 ± 1.2	0.984	0.862
TCHO (mmol/L)	4.8 ± 1.1	4.9 ± 1.3	5.1 ± 1.2	0.351	0.163
HDL-C (mmol/L)	1.0 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	0.007	0.003
LDL-C (mmol/L)	2.7 ± 0.8	2.8 ± 1.0	2.8 ± 0.9	0.645	0.351
Apo A-1 (g/L)	1.3 ± 0.3	1.4 ± 0.3	1.5 ± 0.3	0.009	0.003
Apo B (g/L)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.397	0.176
Calcium† (mmol/L)	2.4 ± 0.2	2.3 ± 0.2	2.4 ± 0.2	0.828	0.633
Phosphorus (mmol/L)	1.8 ± 0.5	1.7 ± 0.5	1.5 ± 0.4	<0.001	<0.001
iPTH (pg/mL)	578.7 ± 439.1	569.3 ± 434.9	551.6 ± 603.3	0.948	0.748
UA (umol/L)	411.9 ± 89.9	406.9 ± 72.3	390.5 ± 68.7	0.223	0.100
GLU (mmol/L)	6.3 ± 3.1	6.1 ± 2.9	5.3 ± 1.4	0.037	0.017
Albumin (g/L)	37.9 ± 3.5	37.7 ± 3.3	37.4 ± 4.3	0.641	0.350
hsCRP (mg/L)	2.1 (0.9, 5.5)	1.8 (0.5, 4.1)	1.0 (0.3, 3.4)	0.352	0.121
ProBNP (pg/mL)	3587.0 (1638.0, 13118.5)	4787.5 (1603.7, 13756.7)	4240.0 (1836.0, 16453.0)	0.177	0.092

†Corrected for serum albumin concentration (correction formula: albumin-corrected calcium [mmol/L] = total calcium [mmol/L] + 0.02 × [40–albumin g/L]). Apo A-1, apolipoprotein A1; Apo B, apolipoprotein B; BMI, body mass index; BP, blood pressure; BSA, body surface area; eGFR, estimated glomerular filtration rate; GLU, serum glucose; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; ProBNP, pro-brain natriuretic peptide; TCHO, total cholesterol; TG, triglycerides; UA, uric acid.

Table 2 | Echocardiographic parameters in end-stage renal disease patients grouped by aortic root diameter/body surface area tertiles ($N = 218$)

Echocardiographic Parameters	Aortic root diameter/BSA tertiles (cm/m^2)			*P*	*P*-trend
	<1.94 ($n = 70$)	1.94–2.12 ($n = 75$)	>2.12 ($n = 73$)		
LAi (mm/m^2)	23.8 ± 3.8	24.3 ± 3.6	25.0 ± 3.6	0.169	0.061
LVDdi (mm/m^2)	31.2 ± 4.0	32.4 ± 4.6	34.1 ± 4.2	<0.001	<0.001
LVDsi (mm/m^2)	19.8 ± 4.0	20.8 ± 4.9	21.7 ± 3.7	0.024	0.006
LVMi (g/m^2)	157.9 ± 49.7	155.6 ± 43.9	159.4 ± 47.3	0.886	0.845
LVEDVi (mL/m^2)	82.9 ± 25.4	83.9 ± 26.7	84.9 ± 25.8	0.916	0.677
LVESVi (mL/m^2)	30.3 ± 17.9	30.1 ± 17.1	29.5 ± 13.4	0.969	0.810

LAi, left atrium indexed for BSA; LVDdi, left ventricular end-diastolic diameter indexed for BSA; LVDsi, left ventricular end-systolic diameter indexed for BSA; LVEDVi, left ventricular end-diastolic volume indexed for BSA; LVESVi, left ventricular end-systolic volume indexed for BSA; LVMi, Left ventricular mass indexed for BSA.

ARD/BSA. The lower and upper tertiles for ARD/BSA were 1.94 and 2.12, respectively. No significant differences were shown in terms of age, sex, dialysis duration and incidence of hypertension. However, with the increase of ARD/BSA, lower levels of serum creatinine, phosphorus and serum glucose were observed with a linear trend. Furthermore, a lower incidence of diabetes mellitus was shown in patients with greater ARD/BSA. In addition, higher serum HDL-C and apolipoprotein A1 were observed as ARD/BSA increased (Table 1). In Table 2, it is shown that the normalized left ventricular internal measurements in end-diastole (LVDdi) and end-systole (LVDsi) increased with the increase of ARD/BSA.

Echocardiographic parameters in ESRD patients with and without diabetes mellitus

Comparisons were further made between patients with and without diabetes mellitus. In patients with diabetes, lower LVDdi (31.2 ± 4.1 vs 33.1 ± 4.5, $P = 0.005$) and LVDsi (19.7 ± 4.3 vs 21.3 ± 4.2, $P = 0.012$) were noted. Patients with diabetes mellitus also showed lower ARD/BSA (1.9 ± 0.2 vs 2.1 ± 0.2). However, no significant differences were shown neither in absolute ARD nor in ARD normalized for height (ARD/H). In addition, lower early lateral mitral annulus velocity (*e*'), as well as a higher *E*/*e*' ratio, was observed in patients with diabetes (Table 3), indicating worse left ventricular diastolic function in these patients.

Correlation between diabetes mellitus and aortic root dilatation

In the present study, aortic root dilatation was defined as ARD/BSA ≥2.2 cm/m^2 in women or 2.1 cm/m^2 in men. According to Figure 1, the percentage of ARD dilatation was significantly lower in patients with diabetes, when compared with those without diabetes. The difference was more obvious in men (43.59 vs 21.21% in men, 29.87 vs 20.00% in women, $P < 0.05$).

In Figure 2a, different age-related increases of aortic root diameter normalized for height (ARD/H) in patients with or without diabetes were shown. Steeper slopes of the regression lines were observed in patients without diabetes ($r = 0.36$ in

Table 3 | Echocardiographic parameters in ESRD patients with or without diabetes mellitus

Echocardiographic parameters	Diabetes mellitus		*P*
	Without ($n = 155$)	With ($n = 63$)	
LA (mm)	39.2 ± 6.3	40.9 ± 6.2	0.059
LAi (mm/m^2)	24.5 ± 3.9	24.3 ± 3.2	0.746
LVDd (mm)	53 ± 7.1	52.5 ± 7.2	0.656
LVDdi (mm/m^2)	33.1 ± 4.5	31.2 ± 4.1	0.005
LVDs (mm)	34.1 ± 6.8	33.1 ± 7.3	0.340
LVDsi (mm/m^2)	21.3 ± 4.2	19.7 ± 4.3	0.012
IVSd (mm)	12.5 ± 2.2	12.8 ± 1.8	0.214
LVPWd (mm)	11.1 ± 1.9	11.2 ± 1.7	0.757
Relative wall thickness (%)	42.4 ± 8.4	43.2 ± 8.1	0.533
LVEF (%)	64.5 ± 9.3	65.4 ± 10.0	0.554
FS (%)	36.2 ± 6.5	36.6 ± 7.5	0.763
LVM (g)	258.2 ± 88.5	259.5 ± 77.6	0.917
LVMi (g/m^2)	159.6 ± 49.0	152.8 ± 40.6	0.336
LV hypertrophy, *n* (%)	134 (86.5)	53 (84.1)	0.656
LVEDVi (mL/m^2)	84.8 ± 24.9	81.7 ± 28.0	0.451
LVESVi (mL/m^2)	30.0 ± 14.9	29.9 ± 19.0	0.992
Aortic root (cm)	3.3 ± 0.4	3.3 ± 0.4	0.943
Aortic root diameter/height (cm/m)	2.0 ± 0.2	2.0 ± 0.2	0.881
Aortic root diameter/BSA (cm/m^2)	2.1 ± 0.2	1.9 ± 0.2	0.004
E (cm/s)	84.5 ± 30.2	81.8 ± 25.6	0.539
A (cm/s)	91.2 ± 22.1	94.4 ± 29.7	0.454
E/*A* ratio	0.9 ± 0.4	1.2 ± 1.1	0.386
e' (cm/s)	8.2 ± 2.4	6.8 ± 1.9	<0.001
E/*e*' ratio	11.0 ± 5.3	12.7 ± 5.6	0.038

Total $n = 218$. A, atrial velocity wave; E, early velocity wave; *e*', early lateral mitral annulus velocity; IVSd, end-diastolic interventricular septum thickness; LA, left atrium; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVMi, left ventricular mass index; LVPWd, end-diastolic left ventricular posterior wall thickness.

patients without diabetes; $r = 0.12$ in patients with diabetes). Similarly, in Figure 2b, age-related increase of aortic root diameter indexed for BSA (ARD/BSA) was attenuated in patients with diabetes ($r = 0.27$ in patients without diabetes; $r = 0.11$ in patients with diabetes).

To investigate potential variables correlated to ARD/BSA, multiple linear regression analysis was carried out. As a result, age, HDL-C and LVDdi were positively correlated with ARD/BSA, while an inverse correlation was observed between female sex, diabetes, phosphorus and ARD/BSA (Figure 3a). Furthermore, multivariate logistic regression analysis showed that age (odds ratio [OR] 1.037, 95% confidence interval [CI] 1.012–1.063), female sex (OR 0.426, 95% CI 0.215–0.843), diabetes (OR 0.353, 95% CI 0.153–0.817), phosphorus (OR 0.430, 95% CI 0.202–0.915) and LVDdi (OR 1.152, 95% CI 1.062–1.250) were independently correlated with aortic root dilatation in our enrolled patients (Figure 3b).

DISCUSSION

In the present study, ESRD patients with diabetes showed declined ARD/BSA, LVDdi, LVDsi and lateral mitral annulus velocity (*e*'). The lower *e*', as well as the higher *E*/*e*' ratio, in patients with diabetes reflected the impaired left ventricular diastolic function. According to the Cardiovascular Risk factors in Patients with Diabetes – a Prospective study in Primary care study, the *E*/*e*' ratio in middle-aged patients with type 2 diabetes was a strong predictor for cardiovascular events[16]. When adjusted for age, sex and other clinical confounders, diabetes

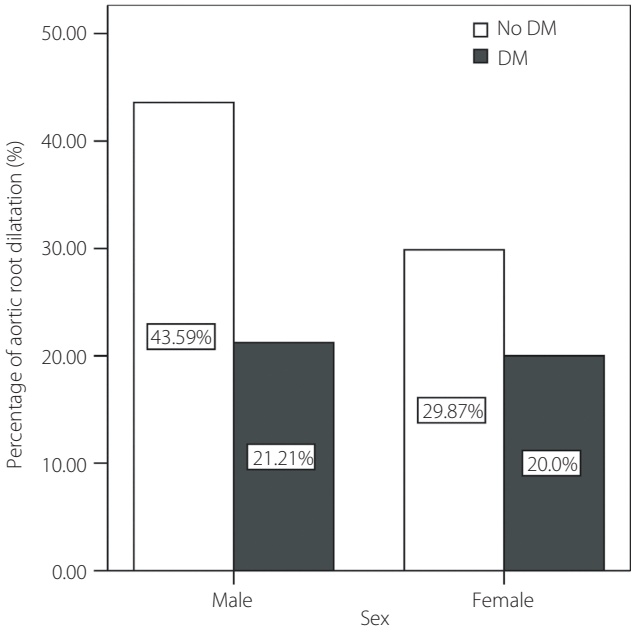

Figure 1 | Percentage of aortic root dilatation in patients with or without diabetes. Aortic root dilatation was defined as aortic root diameter/body surface area ≥2.1 cm/m^2 in women or 2.2 cm/m^2 in men. In patients with diabetes, the percentage of aortic root diameter dilatation was significantly lower, when compared with those without diabetes. The difference was more obvious in men (43.59 vs 21.21% in men, 29.87 vs 20.00% in women, $P < 0.05$). DM, diabetes mellitus.

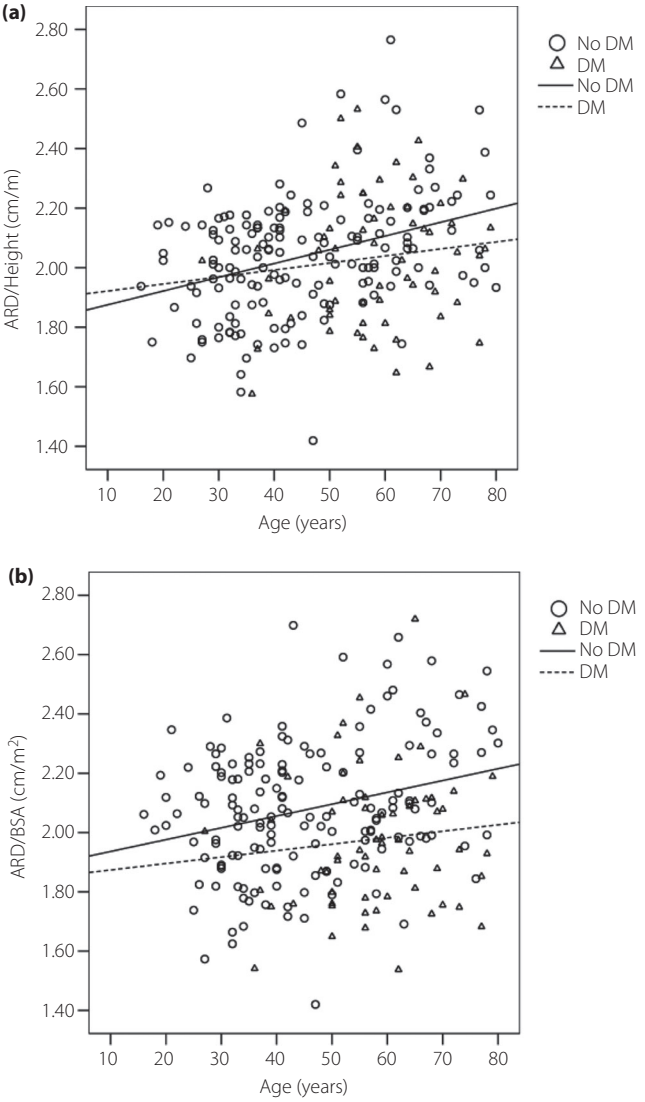

Figure 2 | Age-related increase of aortic root diameter indexed for height (ARD/H) and for body surface area (ARD/BSA) in patients with or without diabetes. (a) The continuous line reflected the age-related increase of ARD/H in patients without diabetes, whereas the dotted line indicated ARD/H increase in diabetes patients. Steeper slopes of the regression lines were observed in patients without diabetes ($r = 0.36$ in patients without diabetes; $r = 0.12$ in patients with diabetes). (b) Similarly, the age-related increase of aortic root diameter indexed for BSA (ARD/BSA) was attenuated in patients with diabetes ($r = 0.27$ in patients without diabetes; $r = 0.11$ in patients with diabetes). The continuous line reflects the age-related increase of ARD/BSA in patients without diabetes, whereas the dotted line shows the ARD/BSA increase in diabetes patients. Steeper slopes of the regression lines were observed in patients without diabetes. DM, diabetes mellitus.

remained to be an independent correlate of aortic root dilatation in ESRD patients.

Previous studies have summarized several factors that might influence aortic dimension, such as age, sex, blood pressure, renal function and so on[17]. According to the Januvia Multicenter Prospective Trial in Type 2 Diabetes study, both the aortic root diameter at the sinus of Valsalva and at the sino-tubular junction increased with age[18]. In the present study, diabetes attenuated the age-related increase of normalized ARD. Additionally, in our enrolled population, factors including age, female sex, diabetes, phosphorus and LVDdi were independently associated with the incidence of aortic root dilatation.

Data from the Chin–Shan Community Cardiovascular Cohort study showed that ARD indexed for BSA was significantly correlated with all-cause mortality in participants aged <65 years[19]. In addition, diabetes mellitus was identified as a crucial cardiovascular risk factor in previous studies. However, results from our studies showed that diabetes exerted favorable effects on ARD, thus it might reduce adverse cardiovascular events to some extent, which was unexpected. There are several possible explanations. For one thing, chronic hyperglycemia was reported to be associated with decreased extracellular matrix and increased extracellular matrix synthesis. Downregulated plasma level of matrix metalloproteinases, reduced monocyte-macrophage interaction, elevated plasminogen activator inhibitor-1 and circulating C-peptide were also reported in patients with diabetes, and thus were involved in the progression of aortic artery stiffness and dilatation[20,21].

For another, patients with diabetes might obtain cardiovascular benefits from various antidiabetic drugs, including metformin, the thiazolidinediones, sulfonylurea, dipeptidylpeptidase-4[22,23]. According to a meta-analysis that included 58,160 patients from 13 randomized controlled trials, slight reduction in major adverse cardiovascular events and myocardial infarction were observed in

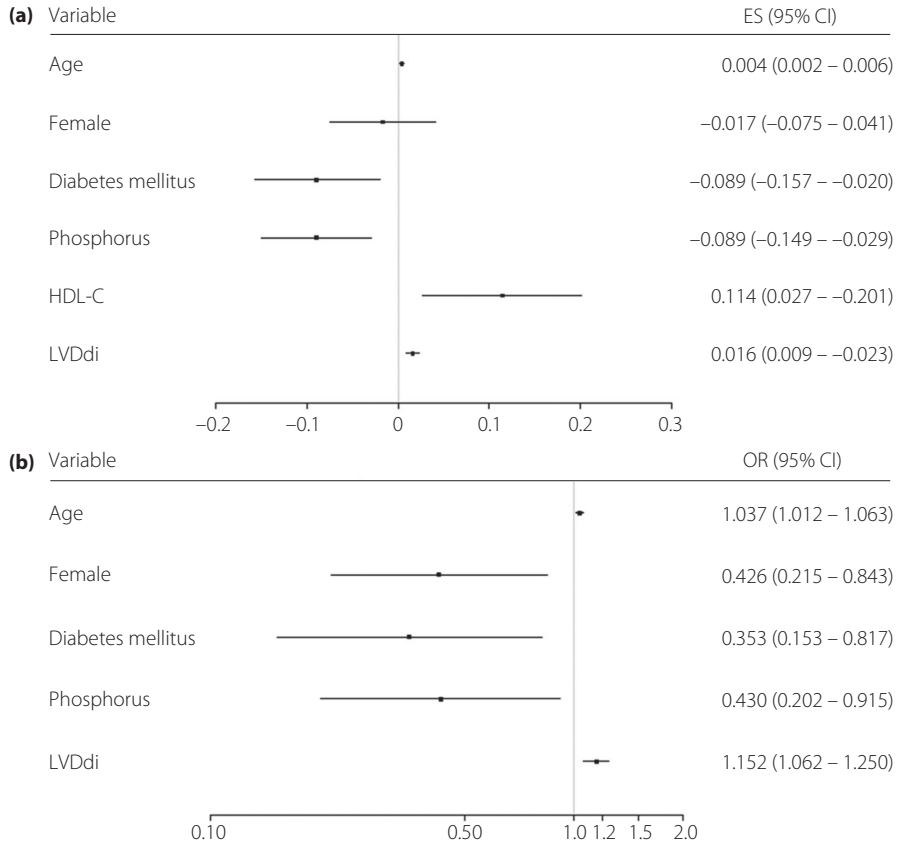

Figure 3 | Multiple linear regression analysis for variables correlated to aortic root diameter (ARD)/body surface area (BSA) and multivariate logistic regression analysis for variables correlated to aortic root dilatation. (a) Age (r = 0.004, 95% confidence interval [CI] 0.002–0.006, $P < 0.001$), high-density lipoprotein cholesterol (HDL-C; r = 0.114, 95% CI 0.027–0.201, P = 0.009) and left ventricular internal measurements in end-diastole (LVDdi; r = 0.016, 95% CI 0.009–0.023, $P < 0.001$) were positively correlated with ARD/BSA, whereas an inverse correlation was observed between female sex (r = –0.017, 95% CI –0.075 to 0.041, P = 0.572), diabetes (r = –0.089, 95% CI –0.157 to –0.020, P = 0.011), phosphorus (r = –0.089, 95% CI –0.149 to –0.029, P = 0.004) and ARD/BSA. (b) Age (odds ratio [OR] 1.037, 95% CI 1.012–1.063, P = 0.003), female sex (OR 0.426, 95% CI 0.215–0.843, P = 0.006), diabetes (0.353, 95% CI 0.153–0.817, P = 0.015), phosphorus (OR 0.430, 95% CI 0.202–0.915, P = 0.028) and LVDdi (OR 1.152, 95% CI 1.062–1.250, P = 0.001) were independently correlated with aortic root dilatation in our enrolled patients. ES, estimate; OR, odds ratio.

patients receiving intensive glucose lowering therapy[24]. Metformin, one of the most prescribed antidiabetic agents, exerted beneficial effects on lipid metabolism through lowering plasma triglycerides. In diabetes patients with cardiovascular diseases, such as myocardial infarction, stable coronary artery disease and so on, metformin treatment led to reducing cardiovascular events and improving left ventricular function[25,26]. As insulin-sensitizing agents, thiazolidinediones promote β-cells to secrete insulin and preserve β-cell function. Furthermore, thiazolidinediones also exert cardiovascular effects through activation of peroxisome proliferator-activated receptors-γ, thus they are involved in regulating lipid profiles, reducing blood pressure and improving endothelial dysfunction[22].

The present study had some advantages. Most previous studies focused on the relationship between diabetes and abdominal aortic aneurysm or thoracic aortic aneurysm. However, only a few studies have investigated the correlation between aortic root dimension with diabetes, and similar studies involving ESRD patients are still lacking. Furthermore, the present study showed the negative effects of diabetes on age-related aortic root dilatation in ESRD patients, which might provide potential therapeutic strategies for cardiovascular protection in this population.

Nevertheless, there were a few limitations. Mainly, this is a single-center study, thus, the results could not be extrapolated to all ESRD patients. Likewise, larger-scale prospective studies are required to investigate the potential effects of diabetes on the prognosis of cardiovascular complications in this population.

DISCLOSURE

The authors declare no conflict of interest.

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