Journal of Diabetes and Its Complications 33 (2019) 623–627

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Increased cardio-ankle vascular index is independently associated with chronic kidney disease: A cross-sectional study in Chinese patients with type 2 diabetes mellitus

Chenghui Zhang, Yajun Zhong, Haoming Tian *

Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu 610041, China

ARTICLE INFO

Article history:
Received 7 February 2019
Received in revised form 8 May 2019
Accepted 11 May 2019
Available online 17 May 2019

Keywords:
Arterial stiffness
Cardio-ankle vascular index
Chronic kidney disease
Type 2 diabetes mellitus
Pulse wave velocity

ABSTRACT

Aims: This cross-sectional study aimed to investigate the association between arterial stiffness and chronic kidney disease (CKD) in Chinese patients with type 2 diabetes mellitus (T2DM).
Methods: This study included 1025 patients with T2DM (796 men, 229 women). The cardio-ankle vascular index (CAVI) served as an index to evaluate arterial stiffness. CKD was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 and/or urinary albumin-creatine ratio ≥ 30 mg/g. Increased CAVI was defined as a value ≥9.
Results: The mean CAVI was 8.4 ± 1.2. Among the patients, 314 (40%) had increased CAVI and 229 (22.3%) had CKD. Blood pressure, HbA1c levels, total cholesterol, low-density lipoprotein cholesterol, uric acid and CAVI were higher among patients with CKD than among those without CKD. Patients with increased CAVI were at a 1.82-fold (95% CI, 1.20–2.75; $P < 0.001$) higher prevalence of CKD after adjusting for other variables. The odds ratio for CKD was 2.69 (95% CI, 1.12–6.47; $P = 0.027$) in women and 1.62 (95% CI, 1.01–2.61; $P = 0.045$) in men.
Conclusion: Increased CAVI was independently associated with CKD in patients with T2DM. Further longitudinal studies with large sample sizes are warranted to investigate the effect of CAVI on CKD in patients with T2DM.

1. Introduction

Chronic kidney disease (CKD) is considered an increasing public health problem.[1] The China National Survey of CKD from 2007 to 2010 revealed that the overall prevalence of CKD in China is 10.8% and that the number of patients with CKD is estimated to be approximately 119.5 million.[2] Diabetes mellitus is recognized as the leading cause of CKD and end-stage renal disease (ESRD), and the incidence of diabetes-related ESRD is increasing at an alarming rate.[3–5] Besides diabetes, hyperglycemia, obesity, smoking status, hypertension, hyperuricemia, and metabolic syndrome are risk factors for CKD, as reported previously.[6–9] Moreover, these factors are also known to be associated with increased arterial stiffness.[10–13] Both CKD and increased arterial stiffness are risk factors for cardiovascular disease and are strong predictors of future cardiovascular events and all-cause mortality.[14–17]

Previous studies have reported that arterial stiffness is associated with incident albuminuria and decreased estimated glomerular filtration rate (eGFR) in both the general population and patients with type 2 diabetes mellitus (T2DM).[18–21] The indices used in these studies included brachial-ankle pulse wave velocity (ba-PWV) and carotid-femoral pulse wave velocity (cf-PWV). Although PWV is widely used as an indicator of arterial stiffness and a marker reflecting vascular damage, PWV has been reported to be affected by several factors, including blood pressure (BP) at the time of measurement and autonomic nerve function.[22] Recently, as a non-invasive index of arterial stiffness, the cardio-ankle vascular index (CAVI) was developed to estimate the degree of stiffness of systemic arteries.[23] CAVI is adjusted for BP based upon the stiffness parameter beta; thus, it is independent of BP.[24] The measurement accuracy of CAVI and its correlation with several arteriosclerotic parameters have been previously reported.[25–27] Evidence shows that CAVI is superior to PWV because its measurement is not affected by BP and CAVI has a high level of reproducibility.[28] Moreover, several studies have been conducted to determine the associations between CAVI and many vascular-related diseases.[29–31]

Furthermore, several studies have found that CAVI is associated with eGFR and CKD in the general population.[32,33] However, few studies have reported the association between arterial stiffness and CKD using CAVI as a stiffness parameter in patients with diabetes. Kim reported that increased CAVI is associated with microvascular complications, such as nephropathy and neuropathy, in patients with T2DM; however, that study included a small number of patients and only used microalbuminuria as a marker of CKD.[34] Herein, we conducted a

Declaration of competing interest: None.

* Corresponding author: 37 Guo Xue Xiang, Chengdu, Sichuan 610041, China.
E-mail address: HaomingTianscu@163.com (H. Tian).

https://doi.org/10.1016/j.jdiacomp.2019.05.009
1056-8727/

large-scale cross-sectional study to investigate the association between CAVI and the prevalence of CKD in Chinese patients with T2DM.

2. Materials and methods

2.1. Subjects

This retrospective cross-sectional study recruited consecutive patients with T2DM aged 18–79 years who were hospitalized for either comprehensive diabetic complication screening or poor blood glucose control at the Department of Endocrinology and Metabolism of our hospital between May 2017 and December 2018. Patients were excluded according to the following criteria: (1) low ankle-brachial index (ABI <0.9) and reported history of cardiovascular disease, including coronary heart disease, congestive heart failure, or stroke; (2) presence of systemic inflammatory or infectious disease; (3) presence of malignant tumor; or (4) incomplete data on CAVI and CKD. A total of 1578 patients were screened. After applying the exclusion criteria, 1025 eligible patients were selected and enrolled. This study was approved by the Ethics Review Committee of West China Hospital, Sichuan University, which waived the requirement for informed consent.

2.2. Assessment of arterial stiffness

CAVI was measured by trained technical staff using a VaseraVS-1500A instrument (Fukuda Denshi, Tokyo, Japan) with patients resting in the supine position. Electrocardiogram electrodes were placed on both wrists, and the cuffs were wrapped around the four extremities. A microphone for detecting heart sounds was placed on the sternal angle. BP and waveforms of the brachial and ankle arteries were measured. Data obtained were analyzed using the 1500A vascular screening system software (Fukuda Denshi). The CAVI value was obtained automatically using the following formula: $CAVI = a[\{2\rho \times 1 / (SBP\text{-}DBP)\} \times \{\ln (SBP/DBP) \times PWV^2\}] + b$ (ρ: density of blood; a and b: constants).[23] The average of the right and left CAVI values was used for the analyses. Increased CAVI was defined as a value ≥9 according to the manufacturer's instruction and previous studies.[35–37]

2.3. Data collection

We evaluated both clinical characteristics (age, weight, height, T2DM duration, smoking status, history of hypertension, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) and biochemical parameters (levels of fasting HbA1c, triglycerides [TG], total cholesterol [TC], high-density lipoprotein cholesterol [HDL—C], low-density lipoprotein cholesterol [LDL-C], fasting blood glucose (FBG), serum creatinine [SCr], and uric acid [UA] and urinary albumin-creatinine ratio [ACR]), collected from the electronic medical records. HbA1c was determined by a method based on high-performance liquid chromatography (HPLC) which was approved by the National Glycohemoglobin Standardization Program (NGSP) (HLC-723 G8, Tosoh Corporation, Japan). Serum lipid-profile, Scr, and UA were measured on an automatic biochemistry analyzer (Modular P800, Roche Diagnostics GmbH, Germany) according to standard laboratory procedures. Urinary albumin and creatinine were used to calculate ACR. Regarding the effect of dehydration on CAVI and estimated glomerular filtration rate (eGFR), for those patients with a level of HbA1c ≥9, insulin or oral antidiabetic drugs were used to control blood glucose. After intensive or moderate glucose control, the FBG and SCr were retested. Then ACR, digital fundus photography, and CAVI were performed.

2.4. Definitions

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. eGFR was calculated using the abbreviated Modification of Diet in Renal Disease Study Group (MDRD) formula modified for Chinese subjects: $186 \times [SCr \times 0.011]^{-1.094} \times age^{-0.203}$ (×0.742 in women) × 1.233 (if Chinese).[38] Hypertension was defined as three documented measurements ≥140/90 mmHg at rest, history of hypertension reported by the patient, or treatment with antihypertensive agents. CKD was defined as eGFR <60 mL/min/1.73 m^2 and/or urinary ACR ≥30 mg/g according to the Kidney Disease Outcome Quality Initiative clinical practice guidelines for CKD.[39]

2.5. Statistical analysis

Distribution of the continuous variables was tested by the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation (SD) when normally distributed or median (interquartile range) when not (diabetic duration, ACR, and TG). Categorical variables were showed as number (percentage). Differences between two groups were examined using Student's *t*-test for normally distributed variables, Mann-Whitney *U* test for those non-normally distributed variables, and chi-square test for categorical variables. Multiple logistic regression analysis was performed to evaluate the associations between CAVI and CKD, with results expressed as odds ratio (OR) and 95% confidence interval (CI). The covariates entered into the model were based on univariate analyses and literature review.[40] Interaction and stratified analyses were conducted according to age, diabetic duration, SBP, DBP, LDL-C, UA, and HbA1c. *P* values <0.05 (two-tailed) were considered statistically significant. All analyses were performed using Empower (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) software.

3. Results

A total of 1025 patients were enrolled in this study (mean age, 54.8 ± 9.6 years; age range, 24–79 years; male/female, 758/267). The characteristics of the study participants are presented in Table 1. Of all

Table 1
Characteristics of the study participants grouped by with and without CKD.

Variables	Overall n = (1025)	Without CKD n = (796)	With CKD n = (229)	*P*-value
Male, n (%)	758 (74.0)	579 (72.7)	179 (78.2)	0.099
Age, years	54.8 ± 9.6	54.2 ± 9.5	57.1 ± 9.6	<0.001
Diabetic duration, years	7.0 (4.0–11.0)	6.0 (3.0–10.0)	10.0 (5.0–14.0)	<0.001
BMI, Kg/m^2	25.7 ± 3.4	25.6 ± 3.3	26.0 ± 3.6	0.096
Current smokers, n (%)	599 (58.4)	456 (57.3)	143 (62.5)	0.163
Hypertension, n (%)	486 (47.4)	326 (41.0)	160 (69.9)	<0.001
SBP, mm Hg	129.3 ± 17.4	126.5 ± 16.3	138.8 ± 19.9	<0.001
DBP, mm Hg	82.5 ± 10.9	81.5 ± 10.4	86.0 ± 11.8	<0.001
HbA1c, %	9.2 ± 2.3	9.1 ± 2.3	9.5 ± 2.2	0.040
TG, mmol/L	1.46 (1.08–2.17)	1.44 (1.07–2.10)	1.51 (1.10–2.35)	0.357
TC, mmol/L	4.48 ± 1.11	4.42 ± 1.04	4.67 ± 1.32	0.003
HDL-C, mmol/L	1.16 ± 0.29	1.15 ± 0.28	1.19 ± 0.32	0.091
LDL-C, mmol/L	2.51 ± 0.88	2.47 ± 0.82	2.64 ± 1.05	0.013
FBG, mmol/L	7.18 ± 1.46	7.15 ± 1.43	7.31 ± 1.58	0.256
UA, μmol/L	366.6 ± 86.1	360.4 ± 85.4	387.9 ± 85.1	<0.001
Scr, μmol/L	68.6 ± 23.5	65.1 ± 13.6	81.0 ± 40.7	<0.001
eGFR, ml/min per 1.73 m^2	113.1 ± 29.1	114.5 ± 26.2	100.2 ± 35.4	<0.001
ACR, mg/g	14.0 (7.0-45.7)	10.2 (6.0–19.9)	215.0 (69.0–445.7)	<0.001
CVAI	8.4 ± 1.2	8.2 ± 1.2	8.9 ± 1.2	<0.001
CAVI ≥9, n (%)	314 (30.6)	201 (25.3)	113 (49.3)	<0.001

Abbreviation: CKD, chronic kidney disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, total triglycerides; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FBG, fasting blood glucose; UA, uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; CAVI, carotid ankle vascular index; ACR, albumin-creatinine-ratio.
Data are shown as mean ± standard deviation, number (percentage) or median (interquartile range).

patients, 229 (22.3%) had CKD. Patients with CKD were older ($P < 0.001$) and had a longer T2DM duration ($P < 0.001$). The proportion of patients with hypertension was also higher among patients with CKD ($P < 0.001$). Levels of SBP ($P < 0.001$), DBP ($P < 0.001$), HbA1c ($P = 0.040$), TC ($P = 0.003$), LDL-C ($P = 0.013$), and UA ($P < 0.001$) were higher in patients with CKD than in those without CKD. CAVI values (8.9 vs. 8.2; $P < 0.001$) and the proportion of patients with increased CAVI (49.3% vs. 25.3%) were also higher among patients with CKD. No significant differences were found in the proportion of smokers, BMI, FBG, TG, and HDL-C between the two groups.

Table 2 compares the characteristics of the normal CAVI and increased CAVI groups. Compared with patients with normal CAVI, those with increased CAVI were older, had a longer T2DM duration, and were more likely to be active smokers and hypertensive. They also had higher levels of SBP, DBP, HDL—C, and UA and worse renal function, but had lower BMI and TG, TC, and LDL-C levels. Fewer patients in the increased CAVI group had all three "ABC" targets (A, HbA1c; B, BP; C, LDL-C) compared with the normal CAVI group, but this difference was not statistically significant (4.1% vs. 6.9%; $P = 0.08$).

Moreover, the unadjusted associations between the clinical variables and CKD risk were analyzed. As shown in Table 3, our results indicate that age ($P < 0.001$), T2DM duration ($P < 0.001$), presence of hypertension ($P < 0.001$), SBP ($P < 0.001$), DBP ($P < 0.001$), TC ($P = 0.003$), LDL-C ($P = 0.014$), UA ($P < 0.001$), HbA1c ($P = 0.027$), and CAVI ($P < 0.001$) were positively associated with CKD. In addition, a positive association was found between BMI and CKD, but this association was not statistically significant.

Table 4 shows the results of the multivariate logistic regression analysis for the associations between CAVI and CKD. In multivariate models including age, T2DM duration, BMI, smoking status, SBP, UA, LDL-C, and HbA1c, the prevalence of CKD increased with increasing CAVI in overall patients (OR, 1.36; 95% CI, 1.11–1.66; $P = 0.003$). For female patients, the OR for CKD tended to increase with increasing CAVI, but the increase was not statistically significant (OR, 1.28; 95% CI, 0.85–1.95; $P = 0.238$).

Table 2
Characteristics of the study participants grouped by normal CAVI and increased CAVI.

Variables	Overall n = (1025)	Normal CAVI n = (711)	Increased CAVI n = (314)	*P*-value
Male, n (%)	758 (74.0)	518 (72.9)	240 (76.4)	0.229
Age, years	54.8 ± 9.6	51.5 ± 8.3	62.3 ± 7.9	<0.001
Diabetic duration, years	7.0 (4.0–11.0)	6.0 (3.0–10.0)	10.0 (6.0–14.0)	<0.001
BMI, Kg/m^2	25.7 ± 3.4	25.9 ± 3.5	25.1 ± 3.0	<0.001
Current smokers, n (%)	599 (58.4)	407 (57.2)	192 (61.2)	0.024
Hypertension, n (%)	486 (47.4)	267 (37.6)	219 (69.8)	<0.001
SBP, mm Hg	129.3 ± 17.4	126.0 ± 16.8	136.7 ± 16.6	<0.001
DBP, mm Hg	82.5 ± 10.9	81.8 ± 10.9	84.0 ± 10.7	0.002
HbA1c, %	9.2 ± 2.3	9.2 ± 2.3	9.2 ± 2.3	0.075
TG, mmol/L	1.46 (1.08–2.17)	1.51 (1.12–2.22)	1.32 (0.98–2.08)	0.014
TC, mmol/L	4.48 ± 1.11	4.51 ± 1.08	4.40 ± 1.18	0.154
HDL-C, mmol/L	1.16 ± 0.29	1.15 ± 0.28	1.20 ± 0.30	0.014
LDL-C, mmol/L	2.51 ± 0.88	2.53 ± 0.84	2.46 ± 0.95	0.013
FBG, mmol/L	7.18 ± 1.46	7.23 ± 1.42	7.06 ± 1.55	0.182
UA, μmol/L	366.6 ± 86.1	365.9 ± 88.8	368.1 ± 79.5	<0.001
Scr, μmol/L	68.6 ± 23.5	65.3 ± 15.2	76.1 ± 34.8	<0.001
eGFR, ml/min per 1.73 m^2	113.1 ± 29.1	115.8 ± 27.2	101.2 ± 30.7	<0.001
ACR, mg/g	14.0 (7.0–45.7)	12.5 (6.2–32.2)	23.1 (9.0–144.4)	<0.001
CKD, n (%)	314 (30.6)	116 (16.3)	113 (36.0)	<0.001
Target achievements, n (%)				
HbA1c < 7%	153 (14.9)	105 (15.7)	48 (16.1)	0.870
BP < 130/80 mmHg	329 (32.1)	266 (37.4)	63 (20.1)	<0.001
LDL-c < 2.6 mmol/L	553 (54.0)	376 (53.4)	177 (56.9)	0.301
At three targets	62 (6.0)	49 (6.9)	13 (4.1)	0.080

Data are shown as mean ± standard deviation, number (percentage) or median (interquartile range).

Table 3
The correlations of various factors with risk for CKD by univariate analysis (n = 1025).

Variables	Odds ratio (95% CI)	*P*-value
Age	1.03 (1.02, 1.05)	<0.001
Male	1.34 (0.95, 1.90)	0.100
Diabetic duration	1.10 (1.07, 1.13)	<0.001
BMI	1.04 (0.99, 1.08)	0.097
Smoking	1.24 (0.92, 1.68)	0.163
Hypertension	3.34 (2.44, 4.58)	<0.001
SBP	1.04 (1.03, 1.05)	<0.001
DBP	1.04 (1.02, 1.05)	<0.001
TG	1.05 (0.95, 1.15)	0.358
TC	1.22 (1.07, 1.39)	0.003
LDL-C	1.23 (1.04, 1.46)	0.014
HDL-C	1.53 (0.93, 2.53)	0.092
HbA1c	1.08 (1.01, 1.15)	0.027
UA	1.00 (1.00, 1.01)	<0.001
CAVI	1.61 (1.40, 1.84)	<0.001

The data are presented as odds ratios (95% confidence intervals) and *P*-value.

However, the OR for CKD was 1.38 (95% CI, 1.10–1.75; $P = 0.006$) for the male patients.

We further evaluated whether increased CAVI was associated with CKD in male and female patients. Patients with increased CAVI had a 1.82-fold (95% CI, 1.20–2.75; $P < 0.001$) greater prevalence of CKD after adjusting for other variables. The OR for CKD was 2.69 (95% CI, 1.12–6.47; $P = 0.027$) for female patients and 1.62 (95% CI, 1.01–2.61; $P = 0.045$) for male patients. These findings suggest that increased CAVI independently associated with the prevalence of CKD.

To further confirm whether there were possible interaction effects on the association of CAVI with CKD risk, stratifies analyses were performed according to the different subgroup, include age (<60 years and ≥60 years), diabetic duration (<10 years and ≥10 years), SBP (<140 mmHg and ≥140 mmHg), DBP (<90 mmHg and ≥90 mmHg), LDL-C (<2.6 mmol/L and ≥2.6 mmol/L), UA (<420 μmol/L and ≥420 μmol/L), and HbA1c (<7%, 7% ≤ HbA1c < 9%, and ≥9%). All analyses were adjusted for age, diabetic duration, BMI, SBP, DBP, LDL-C, UA, and HbA1c except for the variable that was stratified. As shown in Fig. 1, subgroup analyses stratified by different subgroup showed that there was no interaction term between CAVI and CKD (all *P* values >0.05).

4. Discussion

In this cross-sectional study of 1025 patients with T2DM, we examined the association between CAVI and the prevalence of CKD. We found that the prevalence of CKD increased with increasing CAVI in male patients, independent of age and other clinical variables. Patients with

Table 4
Logistic regression analysis of CAVI in relation to CKD risk.

Variables	Female		Male		Total	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CAVI						
Model 1	1.58 (1.19, 2.10)	0.002	1.60 (1.38, 1.87)	<0.001	1.60 (1.40, 1.83)	<0.001
Model 2	1.47 (0.99, 2.18)	0.053	1.69 (1.37, 2.08)	<0.001	1.64 (1.36, 1.97)	<0.001
Model 3	1.28 (0.85, 1.95)	0.238	1.38 (1.10, 1.75)	0.006	1.36 (1.11, 1.66)	0.003
CAVI ≥9						
Model 1	3.81 (2.01, 7.24)	<0.001	2.63 (1.86, 3.72)	<0.001	2.86 (2.11, 3.89)	<0.001
Model 2	3.67 (1.59. 8.44)	0.002	2.23 (1.52, 3.57)	0.001	2.56 (1.75, 3.74)	<0.001
Model 3	2.69 (1.12, 6.47)	0.027	1.62 (1.01, 2.61)	0.045	1.82 (1.20, 2.75)	0.005

The data are presented as odds ratios (95% confidence intervals) and *P*-value. Model 1: non-adjusted; model 2: adjusted for age, diabetes duration, BMI and smoking status; model 3: adjusted for age, duration of DM, BMI, smoking status, SBP, UA, LDL-C and HbA1c.

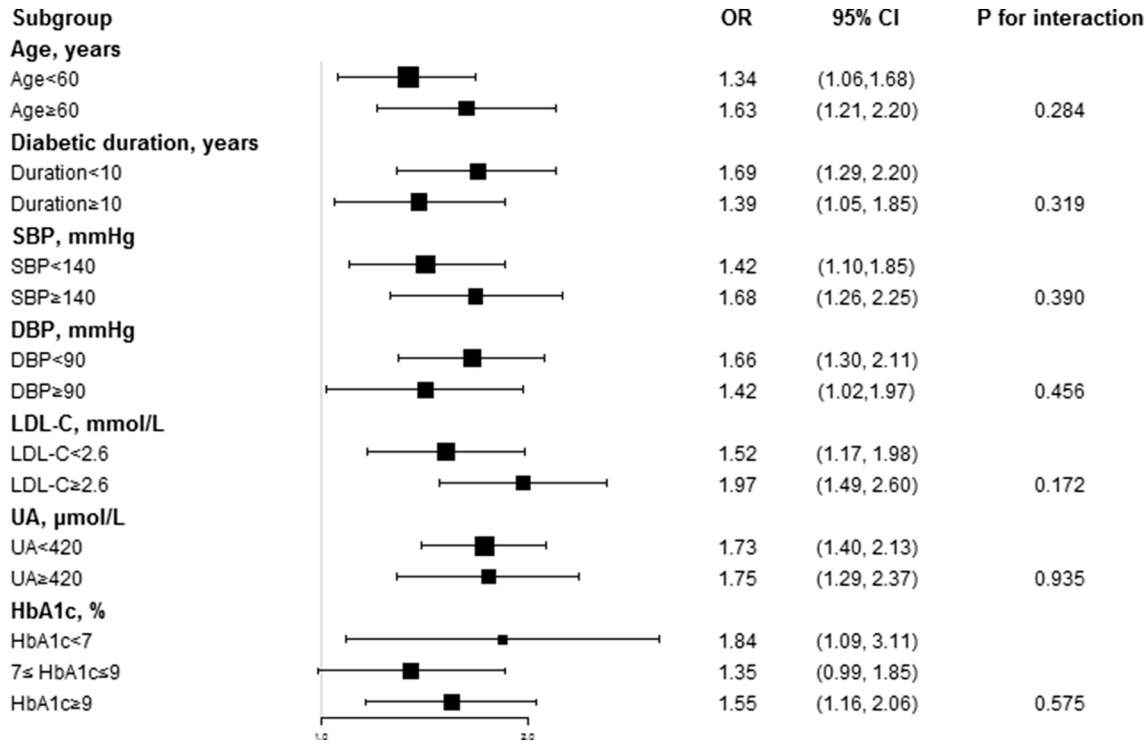

Fig. 1. Association of CAVI and CKD in different subgroup. Each stratification adjusted for all the factors (age, duration of DM, BMI, SBP, DBP, UA, LDL-C and HbA1c) expect the stratification factor itself.

increased CAVI had a 1.82-fold higher prevalence of CKD than those with normal CAVI. Our findings suggest that increased CAVI was independently associated with CKD. To the best of our knowledge, this is the first study using a large group of patients to demonstrate the association between CAVI and CKD in Chinese patients with T2DM.

Previously, current tobacco use, obesity, hypertension, diabetes, and dyslipidemia were identified as risk factors for CKD.[40] Apart from CAVI, our univariate analyses showed that age, T2DM duration, hypertension, SBP, DBP, TC, LDL-C, UA, and HbA1c were associated with CKD. However, the associations among BMI, smoking status, and CKD were not significant. In both observational cohorts and randomized clinical trials, optimal control of multiple risk factors could reduce the micro- and macrovascular complications and mortality rates associated with T2DM. However, among patients with increased CAVI, only 16.1% had HbA1c levels <7%, 20.1% achieved a target BP of <130/80 mmHg, and 56.9% achieved a target LDL-C of <2.6 mmol/L; only 4.1% of patients achieved all three of these targets. Given the increased prevalence of CKD in patients with increased CAVI, anti-stiffness interventions are required in addition to intensive management of glucose, BP, and cholesterol to improve clinical outcomes of cardiovascular and kidney disease.

Several previous reports have assessed the association between arterial stiffness and microalbuminuria and/or eGFR in patients with T2DM. Zhang reported cf-PWV as an independent predictor for albuminuria progression among Asians with T2DM.[20] The REBOUND Study showed that ba-PWV had a stronger association than decreased eGFR with albuminuria in Korean patients with T2DM.[19] While in a longitudinal study, cf-PWV was associated with incident albuminuria and decline rate of eGFR in patients with T2DM.[21] However, the index used in these studies was PWV, which has been reported to be influenced by BP. In our study, we use a different marker to determine the association between arterial stiffness and CKD.

CAVI is considered a parameter to reflect whole arterial stiffness comprising the aorta, femoral artery, and tibial artery and is independent of BP.[41] A previous study reported that in the general population, CAVI was independently correlated with eGFR.[33] Few studies have investigated the relationships between diabetic microvascular complications and arterial stiffness as assessed by CAVI. Lim[34] designed a cross-sectional study of 320 Korean patients with T2DM to evaluate the associations between CAVI and diabetic microvascular complications. They found that increased CAVI was associated with microalbuminuria (OR, 2.47; $P < 0.01$), as well as with peripheral neuropathy (OR, 2.03; $P = 0.03$). Our findings are partially consistent with this study. However, we analyzed a large number of patients and considered the two components of CKD (namely, albuminuria and reduced eGFR), while Lim defined diabetic nephropathy as microalbuminuria.

This study had several limitations. First, this was a retrospective cross-sectional study, which did not confirm the causal relationship between CAVI and CKD. Therefore, a larger-scale prospective study is required to determine the predictive value of CAVI for clinical outcomes (including micro- and macrovascular complications) in patients with T2DM. Second, there may be a potential risk of selection bias since hospitalized patients usually present a more sever clinical features of their disease. Third, the study was performed at a single institution and only involved Chinese patients; therefore, the results might not be generalizable to populations of different ethnicities. Fourth, dehydration was not assessed and that its influence on CAVI was not corrected in this study. Although we underwent CAVI after intensive or moderate glucose control, the current study population was still at high risk of dehydration. Fifth, we did not take into consideration the effects of pharmacological treatment, such as antidiabetic,[42] antiplatelet,[43] antihypertensive,[44] and lipid-lowering drugs,[45] which are known to reduce arterial stiffness.

Nevertheless, the strength of this study is its relatively large sample size involving patients with T2DM. This study provides useful and strong epidemiologic evidence regarding the association between CAVI and CKD in patients with T2DM. In conclusion, CAVI was found to be independently associated with CKD in patients with T2DM. In future, longitudinal studies with larger sample sizes must be conducted to further investigate the effect of CAVI on CKD in patients with T2DM.

Acknowledgements

We thank Editage Company for medical editing assistance with an earlier version of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Eckardt KU, Kasiske BL. Kidney disease: improving global outcomes. Nat Rev Nephro 2014;5:650-7.
2. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet 2012;379:815-22.
3. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850-86.
4. Lea JP, Nicholas SB. Diabetes mellitus and hypertension: key risk factors for kidney disease. J Natl Med Assoc 2002;94:7S-15S.
5. Williams ME. Diabetic CKD/ESRD 2010: a progress report? Semin Dial 2010;23: 129-33.
6. Luk AO, So WY, Ma RC, et al. Metabolic syndrome predicts new onset of chronic kidney disease in 5,829 patients with type 2 diabetes: a 5-year prospective analysis of the Hong Kong Diabetes Registry. Diabetes Care 2008;31:2357-61.
7. Fan F, Qi L, Jia J, et al. Noninvasive central systolic blood pressure is more strongly related to kidney function decline than peripheral systolic blood pressure in a Chinese community-based population. Hypertension 2016;67:1166-72.
8. Othman M, Kawar B, El Nahas AM. Influence of obesity on progression of non-diabetic chronic kidney disease: a retrospective cohort study. Nephron Clin Pract 2009;113:c16-23.
9. Rodenbach KE, Schneider MF, Furth SL, et al. Hyperuricemia and progression of CKD in children and adolescents: the chronic kidney disease in children (CKiD) cohort study. Am J Kidney Dis 2015;66:984-92.
10. Henry RM, Kostense PJ, Spijkerman AM, et al. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. Circulation 2003;107:2089-95.
11. Wallace SM, Yasmin MCM, et al. Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. Hypertension 2007;50:228-33.
12. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R, Yamakado M. Higher serum uric acid is associated with increased arterial stiffness in Japanese individuals. Atherosclerosis 2007;192:131-7.
13. Pal S, Radavelli-Bagatini S. Association of arterial stiffness with obesity in Australian women: a pilot study. J Clin Hypertens 2013;15:118-23.
14. Meisinger C, Döring A, Löwel H. KORA study group. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. Eur Heart J 2006;27: 1245-50.
15. Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005;111:3384-90.
16. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam study. Circulation 2006;113:657-63.
17. Kubota Y, Maebuchi D, Takel M, et al. Cardio-ankle vascular index is a predictor of cardiovascular events. Artery Res 2011;5:91-6.
18. Seo JY, Kim MK, Choi BY, Kim YM, Cho SI, Shin J. Elevated brachial-ankle pulse wave velocity is independently associated with microalbuminuria in a rural population. J Korean Med Sci 2014;29:941-9.
19. Kim JH, Kim SS, Kim IJ, et al. Arterial stiffness is more associated with albuminuria than decreased glomerular filtration rate in patients with type 2 diabetes mellitus: the REBOUND study. J Diabetes Res 2017;2017:1-6.
20. Zhang X, Low S, Sum CF, et al. Arterial stiffness is an independent predictor for albuminuria progression among Asians with type 2 diabetes – a prospective cohort study. J Diabetes Complicat 2017;31:933-8.
21. Bouchi R, Babazono T, Mugishima M, et al. Arterial stiffness is associated with incident albuminuria and decreased glomerular filtration rate in type 2 diabetic patients. Diabetes Care 2011;34:2570-5.
22. Yambe T, Yoshizawa M, Saijo Y, et al. Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). Biomed Pharmacother 2004;58:S95-8.
23. Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb 2006;13:101-7.
24. Ibata J, Sasaki H, Kakimoto T, et al. Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. Diabetes Res Clin Pract 2008;80:265-70.
25. Takaki A, Ogawa H, Wakeyama T, et al. Cardio-ankle vascular index is a new noninvasive parameter of arterial stiffness. Circ J 2007;71:1710-4.
26. Sun CK. Cardio-ankle vascular index (CAVI) as an indicator of arterial stiffness. Integr Blood Press Control 2013;6:27-38.
27. Shirai K, Hiruta N, Song M, et al. Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: theory, evidence and perspectives. J Atheroscler Thromb 2011;18:924-38.
28. Takaki A, Ogawa H, Wakeyama T, et al. Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res 2008;31:1347-55.
29. Saiki A, Sato Y, Watanabe R, et al. The role of a novel arterial stiffness parameter, cardio-ankle vascular index (CAVI), as a surrogate marker for cardiovascular diseases. J Atheroscler Thromb 2016;23:155-68.
30. Satoh-Asahara N, Kotani K, Yamakage H, et al. Cardio-ankle vascular index predicts for the incidence of cardiovascular events in obese patients: a multicenter prospective cohort study (Japan Obesity and Metabolic Syndrome Study: JOMS). Atherosclerosis 2015;242:461-8.
31. Qiao A, Song X, Peng K, Du G, Li G, Chen Z. Validity of CAVI measurements for diagnosing hypertension in middle-aged and elderly patients and correlations of these measurements with relevant factors. Technol Health Care 2017;25:125-34.
32. Maebuchi D, Sakamoto M, Fuse J, et al. The cardio-ankle vascular index predicts chronic kidney disease in Japanese subjects. Artery Res 2013;7:48-53.
33. Kubozono T, Miyata M, Ueyama K, et al. Association between arterial stiffness and estimated glomerular filtration rate in the Japanese general population. J Atheroscler Thromb 2009;16:840-5.
34. Kim KJ, Lee BW, Kim HM, et al. Associations between cardio-ankle vascular index and microvascular complications in type 2 diabetes mellitus patients. J Atheroscler Thromb 2011;18:328-36.
35. CAVI: Fukuda-Denshi Company L, Tokyo, Japan. http://www.fukuda.co.jp/english/products/special_features/vasera/cavi.html. Accessed March 27, 2019.
36. Nakamura K, Tomaru T, Yamamura S, et al. Cardio-ankle vascular index is a candidate predictor of coronary atherosclerosis. Circ J 2008;72:598-604.
37. Chung SL, Yang CC, Chen CC, et al. Coronary artery calcium score compared with cardio-ankle vascular index in the prediction of cardiovascular events in asymptomatic patients with type 2 diabetes. J Atheroscler Thromb 2015;22:1255-65.
38. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006;17: 2937-44.
39. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089-100.
40. Whaley-Connell AT, Sowers JR, Mcfarlane SI, et al. Diabetes mellitus in CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition and Examination Survey (NHANES) 1999–2004. Am J Kidney Dis 2008;51:S21-9.
41. Shirai K, Utino J, Saiki A, et al. Evaluation of blood pressure control using a new arterial stiffness parameter, cardio-ankle vascular index (CAVI). Curr Hypertens Rev 2013;9:66-75.
42. Batzias K, Antonopoulos AS, Oikonomou E, et al. Effects of newer antidiabetic drugs on endothelial function and arterial stiffness: a systematic review and meta-analysis. J Diabetes Res 2018, 1232583, https://doi.org/10.1155/2018/1232583.
43. Pietri P, Vlachopoulos C, Terentes-Printzios D, et al. Beneficial effects of low-dose aspirin on aortic stiffness in hypertensive patients. Vasc Med 2014;19:452-7.
44. Katsiki N, Imprialos K, Vlachopoulos C. Editorial: arterial stiffness, central haemodynamics and non-alcohilic fatty liver disease: links with cardiovascular risk and effects of drug treatment. Curr Vasc Pharmacol 2018;16:401-4.
45. Reklou A, Katsiki N, Karagiannis A, et al. Effects of lipid lowering drugs on arterial stiffness. One more way to reduce cardiovascular risk? Curr Vasc Pharmacol 2019, https://doi.org/10.2174/1570161117666190121102323.