Kidney & Blood Pressure Research

Kidney Blood Press Res 2018;43:1479-1487

DOI: 10.1159/000493663
Published online: 21 September, 2018

Accepted: 12 September, 2018

Original Paper

Gender Difference in the Relationship of Albuminuria and Arterial Stiffness in Chinese Adults - a 6.6-Year Follow-Up Longitudinal Study

Ching-Chun Lin[a,d] Kuo-Tung Tang[c] Chia-Ing Li[b,d] Chiu-Shong Liu[a,d] Ming-May Lai[a,d] Wen-Yuan Lin[a,d,e] Cheng-Chieh Lin[a,d]

[a]Department of Family Medicine, China Medical University Hospital, Taichung, [b]Medical Research, China Medical University Hospital, Taichung, [c]Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, [d]Department of Family Medicine, School of Medicine, College of Medicine, China Medical University, Taichung, [e]Social Medicine, School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

Key Words
Albuminuria • Circulatory disease • Epidemiology • Gender

Abstract
Background/Aims: Brachial–ankle pulse wave velocity (baPWV) reflects the stiffness of muscular arteries. Albuminuria is recognized as a marker of vascular dysfunction. We assessed the association between arterial stiffness and albuminuria in a population-based longitudinal study. ***Methods:*** 1116 adults aged ≥ 40 years in the Taichung Community Health Study (TCHS) in 2004 attended a follow-up visit in 2011. Albuminuria was defined as an urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g. Arterial stiffness was defined as BaPWV ≥ 1540 cm/sec in males and BaPWV ≥ 1480 cm/sec in females, respectively. ΔbaPWV was calculated as baPWV at follow-up minus baPWV at baseline, while ΔUACR was calculated as UACR at follow-up minus UACR at baseline. Multiple linear and logistic regression analyses were used to explore the relationship between albuminuria and arterial stiffness. ***Results:*** Among 652 subjects without arterial stiffness at baseline, 209 (32%) subjects developed incident arterial stiffness after an average of 6.6 years. In male subjects, baseline albuminuria was associated with development of arterial stiffness (odds ratio: 4.47, 95% confidence interval [CI]: 1.04–19.31) and ΔbaPWV was modestly positively associated with ΔUACR. ***Conclusion:*** Our results indicated that male adults with albuminuria had an increased risk for developing arterial stiffness.

C. Lin and K.Tung Tang contributed equally to this work.

Cheng-Chieh Lin
and Wen-Yuan Lin

Department of Family Medicine, China Medical University Hospital
2, Yuh-Der Road, Taichung 40447 (Taiwan)
Tel. +886-4-22052121, E-Mail cclin@mail.cmuh.org.tw; wylin@mail.cmu.edu.tw

Introduction

Cardiovascular disease (CVD) is a leading cause of death worldwide [1] and recognized as a major public health challenge. Arterial stiffness has been proposed as an important risk factor for CVD, contributing to its development and mortality [2, 3]. Brachial–ankle pulse wave velocity (baPWV) measurement is a simple, noninvasive examination that reflects the stiffness of both central and peripheral muscular arteries [4]. BaPWV has also shown a good correlation with aortic PWV, which reflects vascular damage [4]. Many studies have demonstrated that baPWV is useful for identifying arterial atherosclerotic changes in patients with both clinical and subclinical disease [5-8]. Furthermore, Kitahara et al. reported that in hemodialysis patients without advanced peripheral arterial occlusive disease, those with higher baPWV have increased cardiovascular and all-cause mortality [9]. Albuminuria is associated with a greater risk for future cardiovascular disease and cardiovascular/ all-cause mortality [10-12]. However, the mechanism relating albuminuria to increased risk for CVD is not well understood. It has been suggested that arterial stiffness is the underlying mechanism [13]. Our previous study demonstrated that albuminuria is strongly related to arterial stiffness among Chinese middle-aged adults in a cross-sectional analysis based on the Taichung Community Health Study (TCHS) [14]. We hypothesized that albuminuria is associated with future development of arterial stiffness. Therefore, we followed subjects in the TCHS to assess the association between albuminuria and arterial stiffness longitudinally in a population-based study.

Materials and Methods

Subjects

Enrollment of study subjects in the TCHS has been described in detail in previous studies [14, 15]. The target population consisted of residents of Taichung City in Taiwan who were aged 40 years or above in October 2004. Two-stage sampling was undertaken to identify residents, with sampling rate proportional to size within each stage. A total of 4280 subjects were selected and 750 of them were ineligible for this study and excluded from the study sample. The reasons for ineligibility were death (n = 18), hospitalization or imprisonment (n = 14), living abroad (n = 39), moving out of the area (n = 411), living in their children's home (n = 7), sampling frame mistakes (n = 59), and not being at home during 3 visits made by interviewers (n = 202). Among the 3530 selected subjects, 2359 agreed to participate and signed the written informed consent form. There was no difference between responders and non-responders regarding age and sex. In addition, subjects with an ankle–brachial index < 0.9 or incomplete data for the urine albumin test and/or baPWV examination were excluded. Urinary creatinine (Jaffe's kinetic method) and albumin (colorimetry bromocresol purple) were measured with an autoanalyzer. The interassay precision coefficient of variation was < 3.0% for both creatinine and albumin concentrations. Albuminuria was defined as an urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g [13]. BaPWV was measured in the morning, with subjects in the supine position and with a VP-1000 automated PWV/ABI analyzer (PWV/ABI; Colin Co. Ltd., Komaki, Japan). Arterial stiffness was defined as in our previous study [16]: BaPWV ≥ 1540 cm/sec in males and BaPWV ≥ 1480 cm/sec in females respectively. In the follow-up study, these subjects were contacted and invited for a follow-up visit in 2011. Finally, 1116 (51%) subjects, comprising 464 individuals with baseline arterial stiffness and 652 individuals without baseline arterial stiffness, attended a follow-up visit. ΔbaPWV was calculated as baPWV at follow-up minus baPWV at baseline, while ΔUACR was calculated as UACR at follow-up minus UACR at baseline. Ethics approval for patient recruitment and data analyses was obtained from the Institutional Review Board of China Medical University Hospital according to the Declaration of Helsinki.

Anthropometric index and laboratory assays

Trained staff measured height, weight, pulse rate and blood pressure (BP) as reported in our previous study [17]. BMI was calculated as weight divided by height squared (kg/m2). Renal function was evaluated by estimated glomerular filtration rate (eGFR), which was calculated using the CKD-EPI equation [18].

Sociodemographic factors and lifestyle behaviors

Age, gender, and physical activity status were collected by self-administered questionnaires. Past major medical history, such as diabetes mellitus, hypertension and hyperlipidemia, and medication history were also collected by questionnaires. Five subjects did not answer the question regarding past diabetes mellitus; 3 subjects did not answer the question regarding past hypertension; 8 subjects did not answer the question regarding past hyperlipidemia. Smoking and alcohol drinking history were divided into 3 classes: never, former, and current; while physical activity status was divided into 2 classes: never/seldom and current.

Statistical analysis

The numerical data are presented as means and standard deviation unless specified otherwise. Student's t-test was used to compare mean values. The Chi-square test was used to compare between categorical variables. Multiple logistic and linear regression analyses were used to evaluate the associations between albuminuria and baPWV with adjustment for potential confounders. A two-tailed *p* value less than 0.05 was considered statistically significant. These statistical analyses were performed using SPSS statistical software (13th version, SPSS Inc., Chicago, IL, USA).

Results

Table 1 compared the characteristics of subjects with arterial stiffness (n=464) and without arterial stiffness (n=652) at baseline. Age, the percentage of men, pulse rate, BMI, the proportion of diabetes mellitus, hypertension and hyperlipidemia, UACR, baPWV, and eGFR were increased in subjects with arterial stiffness when compared with subjects without arterial stiffness at baseline. In addition, current physical activity was more prevalent while alcohol drinking was less prevalent in subjects with arterial stiffness at baseline. Among those without arterial stiffness at baseline, male subjects were older, had higher pulse rate, BMI, baPWV, and proportion of diabetes mellitus, hypertension, hyperlipidemia, and smokers, and had lower eGFR than female subjects (Table 2).

After an average of 6.6 years, 209 (32%) subjects without arterial stiffness at baseline developed incident arterial stiffness at the follow-up visit. Subjects who developed arterial stiffness were older, had higher UACR, baPWV, proportion of diabetes mellitus, and hypertension, and had lower eGFR at baseline and the follow-up visit, and higher pulse rate at the follow-up visit than those subjects who did not (Table 3-4).

Table 1. Baseline characteristics between subjects with arterial stiffness (n=464) and without arterial stiffness (n=652). Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; eGFR: estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio. Arterial stiffness was defined as follows: BaPWV ≧ 1540 cm/sec and BaPWV ≧ 1480 cm/sec in male and female respectively. *p<0.05; **p<0.001

Parameter	Subjects with arterial stiffness (n = 464)	Subjects without arterial stiffness (n = 652)
Age (years)	60.8 ± 9.7	50.1 ± 7.1**
Men (n, %)	241 (45.1%)	293 (54.9%)*
Pulse rate (/min)	69.3 ± 10.3	65.9 ± 8.9**
BMI (kg/m2)	24.4 ± 3.3	23.9 ± 3.1*
UACR (mg/g)	32.4 ± 134.1	8.2 ± 25.0**
baPWV (cm/s)	1845.4 ± 324.7	1297.1 ± 137.7**
eGFR (mL/min/1.73 m2)	83.5 ± 16.5	93.1 ± 15.6**
Diabetes mellitus	11.0%	3.7%**
Hypertension	41.0%	10.4%**
Hyperlipidemia	20.5%	11.0%**
Smoking		
Never	75.4%	76.5%
Current	13.6%	14.3%
Former	10.8%	9.2%
Alcohol drinking*		
Never	76.1%	69.0%
Current	20.0%	26.4%
Former	3.9%	4.6%
Physical activity*		
Never/Seldom	25.2%	33.6%
Current	74.8%	66.4%

Table 2. Characteristics of male and female subjects without arterial stiffness at baseline. Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; eGFR: estimated glomerular filtration rate; NA, not applicable; UACR, urine albumin-to-creatinine ratio. Arterial stiffness was defined as follows: BaPWV ≧ 1540 cm/sec and BaPWV ≧ 1480 cm/sec in male and female respectively. * p<0.05; **p<0.001

Parameter	Male subjects (n = 293)	Female subjects (n = 359)
Age (years)	51.2 ± 7.8	49.3 ± 6.4*
BMI (kg/m2)	24.8 ± 3.0	23.1 ± 3.0**
Pulse rate	64.7 ± 8.6	66.8 ± 9.0*
UACR (mg/g)	8.8 ± 33.6	7.8 ± 14.5
baPWV (cm/s)	1339.2 ± 133.4	1262.6 ± 131.7**
eGFR (mL/min/1.73 m2)	86.3 ± 16.5	98.6 ± 12.3**
Diabetes mellitus	5.8%	1.9%*
Hypertension	13.3%	8.1%*
Hyperlipidemia	16.4%	6.7%**
Menopause	NA	40%
Smoking**		
Never	52.2%	96.4%
Current	28.0%	3.1%
Former	19.8%	0.6%
Alcohol drinking**		
Never	52.6%	82.5%
Current	38.6%	16.4%
Former	8.9%	1.1%
Physical activity		
Never/Seldom	33.8%	33.4%
Current	66.2%	66.6%

Table 3. Baseline characteristics between subjects who developed arterial stiffness (n=209) and who did not (n=443). Abbreviations: BMI, body mass index; eGFR: estimated glomerular filtration rate; baPWV, brachial-ankle pulse wave velocity; UACR, urine albumin-to-creatinine ratio. Arterial stiffness was defined as follows: BaPWV ≧ 1540 cm/sec and BaPWV ≧ 1480 cm/sec in male and female respectively. *p<0.05; **p<0.001

Parameter	Subjects who developed arterial stiffness (n = 209)	Subjects who did not develop arterial stiffness (n = 443)
Age (years)	53.8 ± 7.7	48.4 ± 6.2**
Men (n, %)	94 (32.1%)	199 (67.9%)
Pulse rate (/min)	66.4 ± 8.4	65.6 ± 9.1
BMI (kg/m2)	24.1 ± 3.2	23.7 ± 3.0
UACR (mg/g)	11.9 ± 38.3	6.5 ± 14.8*
baPWV (cm/s)	1377.6 ± 106.2	1259.1 ± 134.6**
eGFR (mL/min/1.73 m2)	89.6 ± 17.2	94.7 ± 14.5**
Hypertension**		
No	82.2%	93.0%
Yes	17.8%	7.0%
Hyperlipidemia		
No	86.8%	89.7%
Yes	13.2%	10.3%
Diabetes mellitus**		
No	92.3%	98.2%
Yes	7.7%	1.8%
Smoking		
Never	75.5%	77.0%
Current	14.4%	14.2%
Former	10.1%	8.8%
Alcohol drinking		
Never	70.3%	68.4%
Current	25.4%	26.9%
Former	4.3%	4.7%
Physical activity		
Never/Seldom	30.1%	35.2%
Current	69.9%	64.8%

Table 4. Characteristics at the follow-up visit between subjects who developed arterial stiffness (n=209) and who did not (n=443). Abbreviations: BMI, body mass index; eGFR: estimated glomerular filtration rate; baPWV, brachial-ankle pulse wave velocity; UACR, urine albumin-to-creatinine ratio. Arterial stiffness was defined as follows: BaPWV ≧ 1540 cm/sec and BaPWV ≧ 1480 cm/sec in male and female respectively. *p<0.05; **p<0.001

Parameter	Subjects who developed arterial stiffness (n = 209)	Subjects who did not develop arterial stiffness (n = 443)
Men (n, %)	94 (32.1%)	199 (67.9%)
Pulse rate (/min)	70.9 ± 10.2	66.8 ± 8.8**
BMI (kg/m2)	24.3 ± 3.3	24.0 ± 3.1
UACR (mg/g)	49.9 ± 236.8	9.8 ± 25.8*
baPWV (cm/s)	1666.9 ± 171.3	1322.0 ± 115.0**
eGFR (mL/min/1.73 m2)	91.3 ± 16.2	96.3 ± 13.3**
Hypertension**		
No	74.2%	87.6%
Yes	25.8%	12.4%
Hyperlipidemia		
No	71.8%	79.2%
Yes	28.2%	20.8%
Diabetes mellitus**		
No	86.1%	94.4%
Yes	13.9%	5.6%
Smoking		
Never	77.1%	78.6%
Current	8.1%	10.8%
Former	14.8%	10.6%
Alcohol drinking		
Never	79.9%	79.4%
Current	17.2%	19.0%
Former	2.9%	1.6%
Physical activity		
Never/Seldom	32.1%	32.7%
Current	67.9%	67.3%

Multiple logistic regression analyses revealed that future development of arterial stiffness was significantly associated with albuminuria at baseline in male subjects, with an odds ratio of 5.16 (95% confidence interval [CI]: 1.55-17.2) in Model 1 (unadjusted) and 4.47 (95% CI: 1.04-19.3) in Model 2 (adjusted for age, BMI, diabetes mellitus, hypertension, hyperlipidemia, eGFR, smoking, alcohol drinking, physical activity status, and menopausal status [in female subjects]) (Table 5), but not in female subjects. In addition, we conducted multiple linear regression analyses among all 1116 subjects who attended the follow-up visit. The results showed that ΔbaPWV was modestly positively associated with ΔUACR in male subjects, with a non-standardized coefficient of 0.167 ± 0.060 ($p < 0.05$) (Table 6), after adjustment for age, BMI, diabetes mellitus, hypertension, hyperlipidemia, eGFR, smoking, alcohol drinking, and physical activity status. However, there was no association between ΔbaPWV and ΔUACR in female subjects.

Table 5. Odds ratios (95% confidence intervals) of having albuminuria at baseline derived from multiple logistic regression analyses using development of arterial stiffness as a dependent variable. Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; eGFR: estimated glomerular filtration rate; UACR, urine albumin-tocreatinine ratio. Arterial stiffness was defined as follows: BaPWV ≧ 1540 cm/sec and BaPWV ≧ 1480 cm/sec in male and female respectively; Normoalbuminuria: UACR < 30 mg/g; albuminuria: UACR ≥ 30 mg/g; reference group is normoalbuminuria. aModel 1, unadjusted; Model 2, adjusted for age, BMI, diabetes mellitus, hypertension, hyperlipidemia, eGFR, smoking, alcohol drinking, physical activity status and menopausal status (in females). *p<0.05

Parameter		Model 1a	Model 2a
Overall	Normoalbuminuria (n = 626)	1.00 (Reference)	1.00 (Reference)
	Albuminuria (n = 26)	1.87 (0.85-4.11)	1.31 (0.53-3.24)
Male	Normoalbuminuria (n = 280)	1.00 (Reference)	1.00 (Reference)
	Albuminuria (n = 13)	5.16 (1.55-17.2)*	4.47 (1.04-19.3)*
Female	Normoalbuminuria (n = 346)	1.00 (Reference)	1.00 (Reference)
	Albuminuria (n = 13)	0.63 (0.17-2.32)	0.42 (0.10-1.74)

Table 6. Multiple linear regression analyses of ΔUACR as a factor associated with ΔbaPWV. Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; eGFR: estimated glomerular filtration rate; SE: standard error; TCHOL, total cholesterol; UACR, urine albumin-tocreatinine ratio. ΔUACR was calculated as UACR at follow-up minus UACR at baseline; ΔbaPWV was calculated as baPWV at follow-up minus baPWV at baseline. aModel 1, unadjusted; Model 2, adjusted for age, BMI, diabetes mellitus, hypertension, hyperlipidemia, eGFR, smoking, alcohol drinking, physical activity status and menopausal status (in females). *p<0.05

Parameter	ΔbaPWV (cm/s)	
	Model 1a	Model 2a
ΔUACR (mg/g)	B ± SE	B ± SE
Men, n = 534	0.158 ± 0.058*	0.167 ± 0.060*
Women, n = 582	0.030 ± 0.072	0.058 ± 0.074

Discussion

This study was a follow-up longitudinal study of the TCHS, a population-based survey of inhabitants in a metropolitan city of central Taiwan. Our results indicated that male adults with albuminuria at baseline had an increased risk for developing arterial stiffness after an average of 6.6 years. In addition, the increase in the amount of albuminuria is positively correlated with the increase of baPWV in male adults, though the correlation was modest. Therefore, screening for albuminuria in men may be of value in the primary prevention of cardiovascular disease.

Epidemiological studies have established the association between albuminuria or renal function and arterial stiffness in hypertensive [19, 20] or diabetic patients [21, 22]. This association was also observed in several cross-sectional studies of the general population [13, 23-25], including the TCHS study [14]. In our population-based longitudinal study, we demonstrated that male adults with albuminuria at baseline have increased risk for developing arterial stiffness. We also found that the increase in the amount of albuminuria was positively correlated with the increase of arterial stiffness in male adults, although the correlation was only modest. This dose-response effect further corroborated our finding, which suggested a relationship between albuminuria and arterial stiffness. It has been postulated that the presence of albuminuria reflects transvascular albumin leakage [26, 27]. Therefore, albuminuria may be an early marker of vascular endothelial dysfunction, which predisposes to the development of atherosclerosis in an individual [28]. The increase of the pulse pressure induced by arterial stiffness further damaged the endothelium, thus creating a vicious cycle, and contributed to the development of albuminuria. In addition, we have previously demonstrated that microalbuminuria is strongly associated with metabolic syndrome (MetS) [17, 24], and MetS is significantly associated with baPWV [16, 29]. Interestingly, endothelial dysfunction has been indicated as an early pathogenic event in MetS [30]. Paapstel et al. also demonstrated that some kidney damage related-cytocines, such as plasma neutrophil gelatinase-associated lipocalin, urinary liver-type fatty acid-binding protein and/or urinary kidney injury molecule-1 are closed related to arterial

stiffness among male coronary artery disease patients [31]. Hence, men with albuminuria should receive regular screening for arterial stiffness and even overt CVD.

Gender influence is one of the most striking characteristics of CVD. Previous studies have demonstrated the gender difference in the prevalence of traditional risk factors for CVD [32, 33], and we also found that male subjects had higher BMI, proportion of diabetes mellitus, hypertension, hyperlipidemia, and smokers than female subjects amongst those without arterial stiffness at baseline. In addition, these male subjects had higher baPWV than female subjects, which is compatible with the higher incidence of CVD in men than in women [34, 35]. Longitudinally, we observed that the association between albuminuria at baseline and future development of arterial stiffness exists in male adults only, even after adjusting for traditional CVD risk factors. In the present study, male subjects were less favorable in several traditional CVD risk factors than female subjects among those without arterial stiffness at baseline. In addition, androgens are known to activate the renin-angiotensin system [36] and testosterone can cause salt and water retention [37], both of which may contribute to endothelial cell injury and increased arterial stiffness. As a result, these male subjects were more prone to the development of atherosclerosis, which may partly explain our observation that the association of albuminuria and arterial stiffness existed only in males.

Primary prevention of CVD can lead to a substantial reduction of mortality [38] and is an important issue in the promotion of public health [39]. Albuminuria has been recognized as a predictor of worse renal or cardiovascular outcome in patients with diabetes mellitus [40, 41] and in the general population [42, 43]. Some authors have thus advocated mass screening for albuminuria [44]. Our findings corroborate the idea that albuminuria screening in the general male population may help identify people at risk for future development of atherosclerosis, and suitable for early implementation of primary prevention measures. Further interventional studies are mandatory.

Our study has some limitations. First, 1064 (49%) subjects in the TCHS were lost to follow-up 6 years later and this attrition bias may have weakened our results. In addition, the small sample size also made our conclusion less robust. In particular, there were only 26 subjects with albuminuria at baseline. However, our results still shed light on this important public health issue. Second, our previous studies demonstrated that both microalbuminuria and baPWV are associated with MetS [16, 17]. Although the major components of metabolic syndrome (large waist circumference, raised triglyceride, reduced high density lipoprotein, raised blood pressure, and raised fasting glucose) were partly incorporated in our regression analyses (BMI, diabetes mellitus, hypertension and hyperlipidemia), we could not totally eliminate the confounding effect of MetS. Third, although carotid-femoral PWV has been considered as the gold-standard in the measurement of arterial stiffness [45], we measured arterial stiffness using baPWV. Compared with other methods, baPWV is easier, non-invasive, and more time-saving [4]. Furthermore, baPWV has been proved to correlate well with central arterial stiffness such as aortic PWV obtained by invasive recording [46], which strongly predicts carotid-femoral PWV. Fourth, the duration of follow-up in our study may not have been long enough to detect arterial atherosclerotic changes since atherosclerosis develops over decades [47]. A cohort study with a longer follow-up is needed.

Conclusion

Our results demonstrated that male adults with albuminuria had an increased risk for developing arterial stiffness after an average of 6.6 years. Therefore, screening for albuminuria in men may identify the at-risk population as the candidate for primary prevention of CVD.

Acknowledgements

This study was financially supported by grants from Ministry of Science and Technology, Taiwan (NSC93-2314-B-039-025, NSC94-2314-B-039-024, NSC96-2628-B-039-011-MY3, NSC99-2628-B-039-007-MY3) and from the Ministry of Health and Welfare, Taiwan (MOHW107-TDU-B-212-123004).

Disclosure Statement

The authors declare no competing interests.

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