Original Paper

Association of Serum Uric Acid with Arterial Stiffness in Peritoneal Dialysis Patients

Xinhui Liu^{a,b,c} Juan Wu^{a,b} Haishan Wu^{a,b} Chunyan Yi^{a,b} Fengxian Huang^{a,b}
Xueqing Yu^{a,b} Xiao Yang^{a,b}

^aDepartment of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, ^bKey Laboratory of Nephrology, Ministry of Health and Guangdong Province, Guangzhou, Guangdong, ^cDepartment of Nephrology, Shenzhen Traditional Chinese Medicine Hospital, Guangzhou University of Chinese Medicine, Shenzhen, Guangdong, China

Key Words

Peritoneal dialysis (PD) • Serum uric acid (SUA) • Arterial stiffness • Brachial-ankle pulse wave velocity (baPWV)

Abstract

Background/Aims: Serum uric acid (SUA) has been proposed as a mediator associated with increased cardiovascular risk and arterial stiffness. However, evidence on the association between SUA and arterial stiffness in peritoneal dialysis (PD) patients is lacking. The aim of this study was to examine the relationship between SUA and arterial stiffness in PD patients. **Methods:** The patients who performed vascular profiler test from January 1, 2014 to October 31, 2016, and with SUA values were enrolled. Arterial stiffness was evaluated by brachial-ankle pulse wave velocity (baPWV). The relationship between SUA and baPWV was tested by multiple linear regression models. **Results:** Of 645 PD patients, mean SUA was 6.80 (± 1.29) mg/dL, mean baPWV was 1713 (± 505) cm/s. In fully adjusted linear regression models, higher SUA was significantly associated with higher baPWV in young [standardized coefficients (β), 0.085; 95% confidence interval (95% CI), 0.013 to 0.130; $P=0.02$] but not in elderly (β , -0.194; 95% CI, -0.774 to 0.093; $P=0.1$) PD patients. In gender-stratified models of young patients, there was a significant association between SUA and baPWV in male (β , 0.115; 95% CI, 0.015 to 0.182; $P=0.02$) but not in female. Male in the highest gender-specific SUA quartile had a higher baPWV than those in the lowest quartile (β , 0.132; 95% CI, 0.011 to 0.209; $P=0.03$). This gender difference was reversed when selecting male patients with lower SUA levels (quartile 1 and 2) and female patients with higher SUA levels (quartile 3 and 4). **Conclusion:** SUA was positively associated with baPWV in young PD patients, and this association was significant in males but not in females, which is possibly explained by the higher SUA level in males than in females.

© 2018 The Author(s)
Published by S. Karger AG, Basel

Introduction

Serum uric acid (SUA) is a well-known marker of cardiovascular disease (CVD) [1], which is the leading cause of death in peritoneal dialysis (PD) patients [2]. Previous study from our PD center demonstrated that elevated SUA level was an independent risk factor for cardiovascular mortality in male but not female PD patients [3]. However, the underlying mechanisms linking SUA to cardiovascular mortality in PD patients remain uncertain.

Arterial stiffness is an indicator of distensibility and compliance of the vessels, and is more pronounced in dialysis patients compared with the general population [4]. Previous studies have reported that arterial stiffness was an independent predictor of adverse cardiovascular outcome and number of hospitalizations for CVD in PD patients [5, 6]. Some scholars proposed that arterial stiffness could be one of the possible mechanisms by which hyperuricemia increases the risk of CVD through a pathway that involves changes in vascular elastic properties, hypertension and organ damage [7]. Many studies have investigated the relationship between SUA and arterial stiffness in various populations with inconsistent findings, including positive association [8], gender-based association [9] or without association [10]. Nonetheless, this relationship has not been reported in PD patients.

In the review of previous studies, the relationship between SUA and arterial stiffness showed significant gender-specific differences [11-13]. We hypothesized that SUA is positively associated with arterial stiffness in PD patients, and this association is different between genders. Therefore, we conducted this cross-sectional study to evaluate the relationship between SUA and arterial stiffness, as measured by brachial-ankle pulse wave velocity (baPWV), in prevalent PD patients, and gender-related differences were further tested.

Materials and Methods

Study population

All continuous ambulatory PD (CAPD) patients who underwent vascular profiler test at the PD center of The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China from January 1, 2014 to October 31, 2016 were included. Inclusion criteria were as follows: age ≥ 18 years at the time of vascular profiler test; survival for at least 90 days from the first PD therapy. Exclusion criteria: insertion of the PD catheter in other hospitals; transfer from permanent hemodialysis (≥ 3 months) or failed renal transplantation; lack of SUA value. The study was conducted in compliance with the ethical principles of the Helsinki Declaration and approved by the Human Ethics Committees of Sun Yat-sen University. As a part of a larger cohort study, written informed consent was obtained from all participants.

Data collection

Demographic data, clinical and biochemical data, and medication information of all included PD patients were collected within 3 months before or after vascular profile test. Measured glomerular filtration rate (mGFR) was calculated from 24-h urine collections and indexed for the body surface area. CVD was defined as a history of myocardial infarction, angina, congestive heart failure, cerebrovascular event, and peripheral vascular disease [14]. The comorbidity score was determined according to the Charlson Comorbidity Index [15]. The values of baPWV were measured by a noninvasive automatic vascular profiler device BP-203RPE III (Omron, Japan) as our previously described [16]. The baPWV was calculated according to the following formula: $\text{baPWV} = (\text{La} - \text{Lb}) / \text{Tba}$, where La was the length from the suprasternal notch to the ankle, Lb was the length from the suprasternal notch to the brachium, and Tba was the time interval between the initial increase in brachial and ankle waveforms. The average value of bilateral baPWV values was used for analysis. Heart rate and blood pressure were also obtained by the same device. The average values of blood pressure of bilateral arms were used for analysis.

Statistical analysis

The results of patient characteristics were expressed as frequencies and percentages for categorical variables, means and standard deviations for normally distributed continuous variables, and medians and interquartile ranges for continuous variables not normally distributed. The associations between SUA and baPWV in PD patients were examined by multiple linear regression models. Variables with $P < 0.05$ in the univariate analysis were picked into multivariate adjusted model according to following principles: referring to previous literature, presenting clinical relevance, and avoiding multicollinearity. Thus, the final fully adjusted variables included age, gender, body mass index, diabetes, CVD, PD vintage, residual urine volume, heart rate, systolic pressure, high sensitivity C-reactive protein, serum albumin, total cholesterol, intact parathyroid hormone, and uric acid-lowering agent use. To further assess the different associations with baPWV at different SUA levels, quartiles of SUA were also built using the lowest SUA quartile as the reference group. The results were expressed as standardized coefficient (β) and 95% confidence interval (95% CI). All analyses in the present study were conducted using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A value of $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 645 prevalent CAPD patients were eligible for present study according to inclusion and exclusion criteria (Fig. 1). The mean ($\pm$ SD) age was 46.6 ± 13.8 years, 89.0% of patients were younger than 65 years, 56.6% of patients were men, 15.7% of patients were diabetic. The primary cause of end-stage renal disease was chronic glomerulonephritis (68.5%), the median PD vintage was 32 months (interquartile range 11 to 58 months). The mean ($\pm$ SD) SUA was 6.80 ± 1.29 mg/dL, the mean baPWV value was 1713 cm/s (Table 1). All patients in our study received CAPD treatment. Conventional PD solutions (Dianeal 1.5%, 2.5% or 4.25% dextrose; Baxter Healthcare, Guangzhou, China), Y sets, and twin bag systems were used in all PD patients. Physiologic calcium peritoneal dialysate (Ca^{2+} concentration = 1.25 mmol/L) was prescribed to all patients in our PD center. As expected, men had significantly higher SUA levels than women (6.95 ± 1.32 mg/dL versus 6.59 ± 1.24 mg/dL, $P < 0.001$). While, there was no significant difference between genders in baPWV values (1715 ± 505 cm/s versus 1710 ± 505 cm/s, $P = 0.9$).

Association of SUA with baPWV

At first, we tested the relationship between SUA and baPWV in total, male, and female patients, respectively. The results indicated that the association between SUA and baPWV was not significant in these patients (Table 2). Since age is a strong determinant of

Fig. 1. The flow chart shows how patients were selected for the present study. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; SUA, serum uric acid.

arterial stiffness [17], we therefore performed subgroup analysis by dividing patients into the elderly group (>65 years) and the young group (≤ 65 years). Unexpected, the data showed that SUA was positively and significantly associated with baPWV in the subgroup of young patients in fully adjusted model (β , 0.085; 95% CI, 0.013 to 0.130; $P=0.02$) (Table 2). We further explored gender-related differences of this association in young patients. The results demonstrated that the association between SUA and baPWV was significant in male (β , 0.115; 95% CI, 0.015 to 0.182; $P=0.02$) but not in female (β , 0.050; 95% CI, -0.039 to 0.124; $P=0.3$) young PD patients (Table 3). To further dissect the association between SUA and baPWV, we stratified young patients in quartiles or gender-specific quartiles of SUA. In total or male young patients, a significant association between the highest quartile of SUA and baPWV was found in fully adjusted models (β , 0.086; 95% CI, 0.002 to 0.142; $P=0.04$; β , 0.132; 95% CI, 0.011 to 0.209; $P=0.03$, respectively). In contrast, the association between SUA and baPWV was not significant in female young patients (Table 3).

To evaluate whether the higher SUA level in male compared with female could explain this gender-specific difference, a sensitivity analyses were performed. According to a previous study higher SUA was associated with greater increase in carotid-femoral PWV in men but not women; this association was lost when men with SUA ≥ 6.2 mg/dL were not included [13], accordingly gender-specific association between SUA and baPWV in our study might be changed by selecting male patients with lower SUA levels and female patients with higher SUA levels. We selected a sample in young PD patients including male in the SUA quartile 1 and 2 (SUA < 6.88 mg/dL) and female in the SUA quartile 3 and 4 (SUA ≥ 6.50 mg/dL). This sample included 164 men and 123 women, with women having significantly higher SUA levels than men (7.58 ± 0.93 mg/dL versus 6.03 ± 0.69 mg/dL, $P < 0.001$). In fully adjusted models, the association between SUA and baPWV became not statistically significant in men (β , 0.072; 95% CI, -0.068 to 0.241; $P=0.3$) but became statistically significant in women (β , 0.202; 95% CI, 0.064 to 0.371; $P=0.006$).

Table 1. Characteristics of study population.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ALP, alkaline phosphatase; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HsCRP, high sensitivity C-reactive protein; iPTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; mGFR, measured glomerular filtration rate; N/L, neutrophil to lymphocyte ratio; PD, peritoneal dialysis

Variables	Study population (n = 645)
Demographics	
Age, y	46.6 $\pm$ 13.8
≤ 65 years	574 (89.0)
> 65 years	71 (11.0)
Male gender	365 (56.6)
Body mass index, kg/m ²	22.4 $\pm$ 3.3
Diabetes	101 (15.7)
Type 1	4 (0.6)
Type 2	97 (15.1)
CVD	275 (42.6)
Primary kidney disease	
Chronic glomerulonephritis	442 (68.5)
Diabetic nephropathy	81 (12.6)
Hypertension	55 (8.5)
Other	67 (10.4)
Charlson comorbidity score	2 (2-3)
PD information	
PD vintage, mo	32 (11-58)
Residual urine volume, mL	400 (50-880)
Kt/V	2.14 (1.77-2.50)
mGFR, mL/min per 1.73m ²	2.90 (0.98-4.67)
Laboratory parameters	
N/L	3.28 (2.48-4.35)
Hemoglobin, g/dL	11.1 $\pm$ 2.0
HsCRP, mg/L	1.52 (0.60-4.58)
ALP, U/L	91 (70-119)
Serum albumin, g/dL	3.66 $\pm$ 0.46
Serum prealbumin, mg/L	385 (323-455)
Corrected calcium, mg/dL	9.56 $\pm$ 0.81
Serum phosphorus, mg/dL	5.11 $\pm$ 1.55
Total cholesterol, mg/dL	193 (166-224)
Triglyceride, mg/dL	132 (92-192)
HDL-C, mg/dL	45 (38-54)
LDL-C, mg/dL	121 (103-146)
Serum urea nitrogen, mg/dL	50 (41-60)
Serum creatinine, mg/dL	11.1 (8.7-14.0)
Serum uric acid, mg/dL	6.80 $\pm$ 1.29
iPTH, pg/mL	303 (156-546)
Vascular profiler data	
Heart rate, bpm	78 $\pm$ 20
Systolic pressure, mmHg	147 $\pm$ 22
Mean arterial pressure, mmHg	116 $\pm$ 18
Diastolic pressure, mmHg	91 $\pm$ 14
baPWV, cm/s	1713 $\pm$ 505
Medications	
Uric acid-lowering agent use	56 (8.7)
Calcium channel blocker use	500 (77.5)
ACEI and/or ARB use	446 (69.1)
Diuretic use	60 (9.3)
Lipid-lowering agent use	131 (20.3)

Discussion

In the present cross-sectional study, we uncovered a significant and positive association between SUA and baPWV in young PD patients. Moreover, this association was significant in males but not in females, which possibly explained by the higher SUA level in males than in females.

Both elevated SUA level and increased arterial stiffness are common and are associated with adverse CVD outcome in PD patients [3, 5, 6]. Many previous studies have investigated the association of SUA with arterial stiffness with inconsistent results [18]. However, this association has not been reported in PD patients. In the present study, we found a positive association between SUA and baPWV in young PD patients. In line with our results, Mehta *et al.* reported that SUA was significantly associated with carotid-femoral PWV (cfPWV) in a younger Caucasian population, utilizing data from participants of the Generation 3 Framingham cohort [19]. However, another study analyzed the data from the Baltimore Longitudinal Study of Aging (BLSA) and found that higher SUA was associated with greater increase in cfPWV in community-dwelling elderly individuals [13]. Another study also reported that SUA was independently and positively associated with baPWV in elderly Chinese with metabolic syndrome components [20]. These different results may be explained by the following reasons. (1) Small sample size of elderly patients. Unlike above mentioned studies focused on elderly population, only 71 (11.0%) patients in present study were older than 65 years. (2) Effect of comorbidity. The study population of previous studies was relatively healthy and had no great comorbidity. However, in our study, elderly patients were more likely to be diabetic (35.2% versus 13.2%, $P < 0.001$) and had higher proportion of CVD history (66.2% versus 39.7%, $P < 0.001$). These comorbidities are associated with arterial stiffness and may weaken the association between SUA and baPWV. Furthermore, in the analysis of young PD patients, our data indicated that the association of SUA

Table 2. Association between SUA and baPWV in total, male, female, elderly, and young PD patients, respectively. ^a Adjusted age, gender, BMI, diabetes, CVD, PD vintage, residual urine volume, heart rate, systolic pressure, HsCRP, serum albumin, total cholesterol, iPTH, and uric acid-lowering agent use. Abbreviations: 95% CI, 95% confidence interval

Variables	β (95% CI) ^a	P Value
Total patients (n = 645)	0.043 (-0.026 to 0.115)	0.2
Male (n = 365)	0.070 (-0.024 to 0.166)	0.1
Female (n = 280)	0.000 (-0.108 to 0.107)	0.9
Elderly patients (n = 71)	-0.194 (-0.774 to 0.093)	0.1
Young patients (n = 574)	0.085 (0.013 to 0.130)	0.02

Table 3. Gender-specific association of SUA with baPWV in young PD patients. ^a Adjusted age, gender, BMI, diabetes, CVD, PD vintage, residual urine volume, heart rate, systolic pressure, HsCRP, serum albumin, total cholesterol, iPTH, and uric acid-lowering agent use. Abbreviations: 95% CI, 95% confidence interval; SUA, serum uric acid

Variables	β (95% CI) ^a	P Value
Continuous SUA		
Male (n = 328)	0.115 (0.015 to 0.182)	0.02
Female (n = 246)	0.050 (-0.039 to 0.124)	0.3
SUA as categorical variable		
Total (n = 574)		
Quartile 1 (≤ 6.05) (n = 143)	Reference	
Quartile 2 (6.05-6.71) (n = 143)	0.074 (-0.007 to 0.128)	0.08
Quartile 3 (6.71-7.59) (n = 145)	0.049 (-0.028 to 0.109)	0.2
Quartile 4 (> 7.59) (n = 143)	0.086 (0.002 to 0.142)	0.04
Male (n = 328)		
Quartile 1 (≤ 6.16) (n = 82)	Reference	
Quartile 2 (6.16-6.88) (n = 82)	0.069 (-0.039 to 0.153)	0.2
Quartile 3 (6.88-7.76) (n = 82)	0.107 (-0.011 to 0.186)	0.08
Quartile 4 (> 7.76) (n = 82)	0.132 (0.011 to 0.209)	0.03
Female (n = 246)		
Quartile 1 (≤ 5.88) (n = 63)	Reference	
Quartile 2 (5.88-6.50) (n = 60)	0.106 (-0.008 to 0.180)	0.07
Quartile 3 (6.50-7.37) (n = 62)	-0.053 (-0.140 to 0.053)	0.4
Quartile 4 (> 7.37) (n = 61)	0.044 (-0.059 to 0.133)	0.4

with baPWV was significant in male but not in female. Many previous studies have displayed this gender-related different association with inconsistent results, which might be related with study design and study population [11-13, 21, 22]. The gender-specific effect of SUA on baPWV we reported here might be due to the higher SUA levels in males. In fact, when we selected a sample of men with lower SUA levels, the significance of the association with baPWV was lost. Thus, it seems that there is a threshold effect for SUA on baPWV, and males cross that threshold more frequently than females. Besides, the duration of exposure to elevated SUA levels may be different between male and female, as SUA levels are generally lower before the menopause [23]. Estrogen is known to promote excretion of uric acid. Previous studies showed that lower SUA levels in female were due to the effect of estrogens on the postsecretory tubular reabsorption of uric acid [24, 25].

The possible mechanisms by which SUA accelerated arterial stiffness have been proposed as follows. First, uric acid stimulates inflammatory pathways by nuclear factor- κ B, Notch-1, and chemoattractant protein 1 signals [26, 27]. Second, uric acid increases production of reactive oxygen species and decreases the bioavailability of nitric oxide in vascular endothelial cells and induces endothelial dysfunction [27, 28]. Third, uric acid activates the local renin-angiotensin system [29]. Forth, uric acid may disturb the natural turnover of non-cross-linked soluble elastin, an important contributor of vascular stiffness [30]. In addition, SUA may interact with conventional and dialysis-specific risk factors in end-stage renal disease patients to promote arterial stiffness progression [31, 32].

There are several advantages in the present study. This study is the first to reveal the association between SUA and arterial stiffness in PD patients. Recognized confounders for SUA and baPWV in the general population and dialysis patients were factored into multivariate linear regression models. However, we are also aware of limitations of this study. First, its cross-sectional design of the study did not allow us to determine a causal relationship. Second, the potential factors associated with SUA and baPWV were not fully investigated. Therefore, the effect of residual confounding cannot be eliminated completely. Third, the sample size of elderly patient in our study is small, so the association between SUA and baPWV in elderly PD patients needs further confirmation. Fourth, we used baPWV as an indicator of arterial stiffness. Generally, cfPWV is recognized as a "gold standard" for evaluating arterial stiffness. However, measurement of cfPWV is operator dependent and time consuming [33]. Alternatively, baPWV is a simple method, just requiring placement of blood pressure cuffs on arm and ankle, and has good reproducibility. It has been showed that baPWV was strongly related with cfPWV and exhibited similar extent of associations with CVD risk factors and clinical events, when compared with cfPWV [34, 35]. Finally, our study participants were all Chinese so our results may not apply to other ethnic groups.

Conclusion

Our data indicated that higher SUA levels was significantly associated with increased baPWV in young PD patients, and this association was restricted to men. This result provides some insight into the mechanism linking SUA to mortality especially CVD mortality in PD patients. Further clinical trials are warranted to test whether lowering SUA levels would be beneficial to prevent arterial stiffness and subsequently CVD outcome.

Acknowledgements

The authors thank all nephrologists and nurses in our PD center for their excellent management of PD patients. This work was supported by the Natural Science Foundation of China (Grant no. 81774069, 81570614, and 81603437), National Key Research and Development Program (Grant no. 2016YFC0906101), the Guangdong Natural Science

Foundation of China (Grant no. 2014A030313139 and S2011010005077), Foundation of Guangdong Key Laboratory of Nephrology (Grant no. 2014B030301023), and the Guangzhou Committee of Science and Technology, China (Grant no. 2014Y2-00543). The funders of this study had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Disclosure Statement

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

- 1 Feig DI, Kang DH, Johnson RJ: Uric acid and cardiovascular risk. *N Engl J Med* 2008;359:1811-1821.
- 2 Mehrotra R, Devuyst O, Davies SJ, Johnson DW: The current state of peritoneal dialysis. *J Am Soc Nephrol* 2016;27:3238-3252.
- 3 Xia X, He F, Wu X, Peng F, Huang F, Yu X: Relationship between serum uric acid and all-cause and cardiovascular mortality in patients treated with peritoneal dialysis. *Am J Kidney Dis* 2014;64:257-264.
- 4 Avramovski P, Janakievska P, Sotirovski K, Sikole A: Accelerated progression of arterial stiffness in dialysis patients compared with the general population. *Korean J Intern Med* 2013;28:464-474.
- 5 Sipahioglu MH, Kucuk H, Unal A, Kaya MG, Oguz F, Tokgoz B, Oymak O, Utas C: Impact of arterial stiffness on adverse cardiovascular outcomes and mortality in peritoneal dialysis patients. *Perit Dial Int* 2012;32:73-80.
- 6 Szeto CC, Kwan BC, Chow KM, Leung CB, Law MC, Li PK: Prognostic value of arterial pulse wave velocity in peritoneal dialysis patients. *Am J Nephrol* 2012;35:127-133.
- 7 Safar ME, London GM: Therapeutic studies and arterial stiffness in hypertension: Recommendations of the European Society of Hypertension. The Clinical Committee of Arterial Structure and Function. Working Group on Vascular Structure and Function of the European Society of Hypertension. *J Hypertens* 2000;18:1527-1535.
- 8 Zhang J, Xiang G, Xiang L, Sun H: Serum uric acid is associated with arterial stiffness in men with newly diagnosed type 2 diabetes mellitus. *J Endocrinol Invest* 2014;37:441-447.
- 9 Bian S, Guo H, Ye P, Luo L, Wu H, Xiao W: Serum uric Acid level and diverse impacts on regional arterial stiffness and wave reflection. *Iran J Public Health* 2012;41:33-41.
- 10 Cicero AF, Salvi P, D'Addato S, Rosticci M, Borghi C: Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: Data from the Brisighella Heart Study. *J Hypertens* 2014;32:57-64.
- 11 Gomez-Marcos MA, Recio-Rodriguez JI, Patino-Alonso MC, Agudo-Conde C, Rodriguez-Sanchez E, Gomez-Sanchez L, Gomez-Sanchez M, Garcia-Ortiz L: Relationship between uric acid and vascular structure and function in hypertensive patients and sex-related differences. *Am J Hypertens* 2013;26:599-607.
- 12 Elsurer R, Afsar B: Serum uric acid and arterial stiffness in hypertensive chronic kidney disease patients: Sex-specific variations. *Blood Press Monit* 2014;19:271-279.
- 13 Canepa M, Viazzi F, Strait JB, Ameri P, Pontremoli R, Brunelli C, Studenski S, Ferrucci L, Lakatta EG, AlGhatrif M: Longitudinal association between serum uric acid and arterial stiffness: Results from the baltimore longitudinal study of aging. *Hypertension* 2017;69:228-235.
- 14 Guo Q, Lin J, Li J, Yi C, Mao H, Yang X, Yu X: The effect of fluid overload on clinical outcome in southern Chinese patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2015;35:691-702.
- 15 Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987;40:373-383.
- 16 Liu X, Zheng X, Yi C, Wu J, Ye H, Guo Q, Yu X, Yang X: Gender-specific associations of skeletal muscle mass and arterial stiffness among peritoneal dialysis patients. *Sci Rep* 2018;8:1351.
- 17 Greenwald SE: Ageing of the conduit arteries. *J Pathol* 2007;211:157-172.

- 18 Ramirez-Sandoval JC, Sanchez-Lozada LG, Madero M: Uric acid, vascular stiffness, and chronic kidney disease: Is there a link? *Blood Purif* 2017;43:189-195.
- 19 Mehta T, Nuccio E, McFann K, Madero M, Sarnak MJ, Jalal D: Association of uric acid with vascular stiffness in the framingham heart study. *Am J Hypertens* 2015;28:877-883.
- 20 Sun N, Zhang Y, Tian JL, Wang H: Relationship between uric acid and arterial stiffness in the elderly with metabolic syndrome components. *Chin Med J (Engl)* 2013;126:3097-3102.
- 21 Fang JI, Wu JS, Yang YC, Wang RH, Lu FH, Chang CJ: High uric acid level associated with increased arterial stiffness in apparently healthy women. *Atherosclerosis* 2014;236:389-393.
- 22 Choi HY, Kim SH, Choi AR, Kim SG, Kim H, Lee JE, Kim HJ, Park HC: Hyperuricemia and risk of increased arterial stiffness in healthy women based on health screening in Korean population. *PLoS One* 2017;12:e180406.
- 23 Hak AE, Choi HK: Menopause, postmenopausal hormone use and serum uric acid levels in US women--the Third National Health and Nutrition Examination Survey. *Arthritis Res Ther* 2008;10:R116.
- 24 Anton FM, Garcia PJ, Ramos T, Gonzalez P, Ordas J: Sex differences in uric acid metabolism in adults: Evidence for a lack of influence of estradiol-17 beta (E2) on the renal handling of urate. *Metabolism* 1986;35:343-348.
- 25 Yahyaoui R, Esteve I, Haro-Mora JJ, Almaraz MC, Morcillo S, Rojo-Martinez G, Martinez J, Gomez-Zumaquero JM, Gonzalez I, Hernando V, Soriguer F: Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab* 2008;93:2230-2233.
- 26 Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikh-Hamad D, Lan HY, Feng L, Johnson RJ: Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 2003;41:1287-1293.
- 27 Xie H, Sun J, Chen Y, Zong M, Li S, Wang Y: EGCG attenuates uric Acid-Induced inflammatory and oxidative stress responses by medicating the NOTCH pathway. *Oxid Med Cell Longev* 2015;2015:214836.
- 28 Kang DH, Park SK, Lee IK, Johnson RJ: Uric acid-induced C-reactive protein expression: Implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol* 2005;16:3553-3562.
- 29 Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML: Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens* 2008;26:269-275.
- 30 Yamanaka H, Osaka M, Takayama M, Munakata K, Nejima J, Katayama M: Age-adjusted level of circulating elastin as a cardiovascular risk factor in medical check-up individuals. *J Cardiovasc Med (Hagerstown)* 2014;15:364-370.
- 31 Nakahigashi M, Tsukaguchi H, Morimoto S, Nakano C, Ueda H, Someya K, Kusabe M, Kikuchi S, Imada T, Shiojima I: Determinants of the change in arterial stiffness in peritoneal dialysis patients. *Int Heart J* 2017;58:915-925.
- 32 Kocyigit I, Sipahioglu MH, Orselik O, Unal A, Celik A, Abbas SR, Zhu F, Tokgoz B, Dogan A, Oymak O, Kotanko P, Levin NW: The association between arterial stiffness and fluid status in peritoneal dialysis patients. *Perit Dial Int* 2014;34:781-790.
- 33 Taal MW: Arterial stiffness in chronic kidney disease: An update. *Curr Opin Nephrol Hypertens* 2014;23:169-173.
- 34 Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T: Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *J Hypertens* 2009;27:2022-2027.
- 35 Tsuchikura S, Shoji T, Kimoto E, Shinohara K, Hatsuda S, Koyama H, Emoto M, Nishizawa Y: Brachial-ankle pulse wave velocity as an index of central arterial stiffness. *J Atheroscler Thromb* 2010;17:658-665.