

Association between age-related kidney function and vascular subclinical state in a healthy Chinese population

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To the Editor: Aging is associated with kidney dysfunction and an increased risk of cardiovascular disease. The connection between the cardiovascular system and kidney function is apparent, even in the early stage of renal insufficiency. Cystatin C (CYSC), one of the cystatin superfamily that is expressed in all the nucleated cells, was considered to be one of the best indicators for evaluating renal function.^[1] CYSC is a potent inhibitor of cathepsin B (CTSB), which is strictly regulated by CYSC in extracellular matrix remodeling. Imbalances between CYSC and CTSB are connected with atherosclerosis (AS), coronary heart disease, and chronic kidney disease with aging-related phenotypes. Our previous study confirmed that serum CTSB levels were associated with age and decreased cardiovascular-renal functions in healthy adults,^[2] suggesting that CTSB exhibits heightened sensitivity to changes in cardiovascular and glomerular function. The present investigation, underlining the role of synthetic and degradative pathways in the aging process, emphasizes that cardio-renal interaction with aging could depend partly on differential expression of some genes leading to an imbalance of functional proteins. In this study, we analyzed the association between renal function, measured by CYSC and estimated glomerular filtration rate (eGFR), and vascular parameters in a healthy Chinese population.

This community-based longitudinal study was begun with the enrollment of subjects in 2008 with follow-up conducted in 2011. In 2008, 501 healthy subjects were confirmed to be study participants out of 1500 volunteers. Following a three-year follow-up, 401 study subjects received the same examinations as were performed in 2008. In this study, we performed a cross-sectional analysis data of 401 subjects in 2011. All subjects were selected based on the results of a physician's questionnaire and clinical biochemical examination. The inclusion criteria were (1) age older than 30 years; (2) being healthy

by self-evaluation; (3) self-care ability; (4) normal social interaction ability and adaptability; and (5) the ability to provide written informed consent. The exclusion criteria were subjects with cardiovascular disease, diabetes, hypertension, and nephropathy, such as nephritis, polycystic kidney, renal tuberculosis, kidney stones, hydro-nephrosis, and ischemic nephropathy. Those previously or currently undergoing therapy that may cause kidney injury were excluded. After excluding individuals for abnormal physical examinations or laboratory tests, a total of 401 healthy subjects (178 men and 223 women) were included in the study. This study was approved by the Medical Ethics Committee of General Hospital of People's Liberation Army, and all subjects provided written informed consent.

Basic parameters, including age, sex, height, and weight, were noted. Blood pressure was measured after the subjects had rested for 10 min. Blood samples were collected at least 10 h after overnight fasting, and blood biochemistry samples, including serum creatinine (SCr), uric acid (UA), fasting blood glucose (FBG), serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were tested with standard assays. The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate eGFR by using SCr levels.

The subjects were placed in a supine position with a neck pillow. The distal wall of the proximal end of the common carotid artery 10 to 15 cm from the beginning of the enlargement was selected. All examinations were performed by the same ultrasonographer blinded to clinical information. The vertical distance between the boundary of lumina-intima and the boundary of intima-adventitia was measured as the intima-media thickness (IMT) of the common carotid artery, and the vertical distance from one side of the intima to the other side of intima was

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determined as the internal diameter (D). We used the color spectrum Doppler mode and asked the subjects to hold their breath while the blood flow spectrum was obtained. The peak systolic blood flow velocity (SPV) and end-diastolic blood flow velocity (EDV) were measured. Measurements were taken over three cardiac cycles and averaged.

All data were analyzed using the SPSS 19.0 statistical software package (SPSS Inc, Chicago, IL, USA). The Kolmogorov-Smirnov method was used for normality testing. The measured data are expressed as mean ± standard deviation, with differences examined using independent-sample *t*-tests. Spearman correlation coefficient test was used to assess the correlation between the two variables. Multiple linear regression analysis was used to examine the effects of confounding factors.

The basic characteristics of the participants were compared according to age and gender [Supplementary Table 1, <http://links.lww.com/CM9/A483>]. Except for diastolic blood pressure (DBP) and HDL, the differences between the other indicators were statistically significant ($P < 0.05$). The elderly exhibited higher SCr, CYSC, UA, IMT, D, carotid intima-medial thickness to diameter (IMT/D), pulsatile index (PI), and resistance index (RI) ($P < 0.05$) and lower eGFR, SPV, and EDV ($P < 0.05$), than young. Except for DBP, IMT/D, and SPV, there were gender differences for the other variables in the same age group. Females had significantly lower levels of SCr,

CYSC, UA, IMT, D, PI, and RI and higher levels of eGFR and EDV ($P < 0.05$).

The subjects' parameters are expressed by tertile of eGFR in Supplementary Table 2, <http://links.lww.com/CM9/A483>. Age, body mass index (BMI), systolic blood pressure (SBP), FBG, SCr, CYSC, UA, TC, LDL, IMT, D, IMT/D, PI, and RI gradually decreased with the progression from low to high eGFR value ($P < 0.05$), whereas HDL, SPV, and EDV gradually increased ($P < 0.05$).

The subjects were divided into three groups according to serum CYSC levels as follows: low concentration group (N = 134 [33.42%]), moderate concentration group (N = 140 [34.91%]), and high concentration group (N = 127 [31.67%]). Age, BMI, SBP, SCr, UA, IMT, D, IMT/D, PI, and RI gradually increased with the progression from low to high CYSC concentration ($P < 0.05$), whereas HDL, eGFR, SPV, and EDV gradually decreased ($P < 0.05$) [Supplementary Table 3, <http://links.lww.com/CM9/A483>].

Supplementary Table 4, <http://links.lww.com/CM9/A483> presents the association between eGFR and clinical and laboratory variables. In all participants, eGFR was correlated with age, SBP, SCr, CYSC, UA, IMT, D, IMT/D, SPV, and EDV. In males, eGFR was correlated with age, SCr, CYSC, UA, cigarette smoking, IMT, IMT/D, SPV, and EDV. In females, eGFR was correlated with age, BMI, SBP, SCr, CYSC, UA, TG, TC, LDL, IMT, D, SPV, and EDV.

Table 1: Correlation of serum CYSC levels with basic characteristics and vascular parameters using r_p (Spearman correlation coefficient).

Items	Total		Male		Female	
	r_p	<i>P</i>	r_p	<i>P</i>	r_p	<i>P</i>
Age	0.535 [†]	<0.001	0.526 [†]	<0.001	0.653 [†]	<0.001
BMI	0.250 [†]	<0.001	0.030	0.727	0.256 [†]	<0.001
Cigarette smoking	0.126 [*]	0.021	-0.029	0.741	0.041	0.568
SBP	0.139 [*]	0.015	0.130	0.128	0.269 [†]	<0.001
DBP	0.038	0.509	0.026	0.765	0.101	0.153
TG	0.180 [†]	0.002	-0.025	0.775	0.307 [†]	<0.001
TC	-0.064	0.266	-0.166	0.052	0.095	0.184
HDL	-0.272 [†]	<0.001	-0.175 [*]	0.041	-0.151 [*]	0.034
LDL	0.022	0.696	-0.100	0.242	0.146 [*]	0.040
FBG	-0.026	0.651	-0.150	0.078	0.045	0.533
SCr	0.571 [†]	<0.001	0.483 [†]	<0.001	0.571 [†]	<0.001
eGFR	-0.739 [†]	<0.001	-0.680 [†]	<0.001	-0.757 [†]	<0.001
UA	0.428 [†]	<0.001	0.224 [†]	0.008	0.461 [†]	<0.001
IMT	0.498 [†]	<0.001	0.481 [†]	<0.001	0.482 [†]	<0.001
D	0.413 [†]	<0.001	0.194 [*]	0.025	0.470 [†]	<0.001
IMT/D	0.248 [†]	<0.001	0.393 [†]	<0.001	0.181 [*]	0.016
SPV	-0.279 [†]	<0.001	-0.252 [†]	0.003	-0.346 [†]	<0.001
EDV	-0.425 [†]	<0.001	-0.364 [†]	<0.001	-0.436 [†]	<0.001
PI	0.187 [†]	0.001	0.169	0.050	0.077	0.295
RI	0.180 [†]	0.001	0.176 [*]	0.041	0.096	0.195

P values are from the ANOVA. * $P < 0.05$; [†] $P < 0.01$. ANOVA: Analysis of variance; BMI: Body mass index; CYSC: Cystatin C; D: Carotid diameter; DBP: Diastolic blood pressure; EDV: End-diastolic velocities; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; HDL: High-density lipoprotein; IMT/D: Carotid intima-medial thickness to diameter; IMT: Carotid intima-media thickness; LDL: Low-density lipoprotein; PI: Pulsatile index; RI: Resistance index; SBP: Systolic blood pressure; SCr: Serum creatinine; SPV: Blood systolic peak velocities; TC: Total cholesterol; TG: Triglyceride; UA: Uric acid.

Overall, serum CYSC was associated with age, BMI, HDL, SCr, eGFR, UA, IMT, D, IMT/D, EDV, and SPV. In men, serum CYSC was associated with age, SCr, UA, IMT, IMT/D, SPV, and EDV. In women, serum CYSC was associated with age, BMI, SBP, TG, SCr, UA, IMT, D, SPV, and EDV [Table 1].

The relationship between eGFR and serum CYSC and vascular markers, determined through multivariate linear stepwise regression analysis after adjustment for parameters associated with eGFR in the pairwise correlation analysis, and the traditional cardiovascular risk factors, is shown in Supplementary Table 5, <http://links.lww.com/CM9/A483>. Overall, eGFR levels were still significantly associated with D, EDV ($P < 0.05$), and PI ($P < 0.01$) after full adjustment. In males, eGFR exhibited significant and independent association with SPV, EDV, PI ($P < 0.01$), and RI ($P < 0.05$).

Overall, CYSC remained significantly associated with IMT/D after adjusting for age and all confounding variables ($P < 0.01$). In females, CYSC showed significant and independent associations with IMT/D ($P < 0.01$) [Supplementary Table 6, <http://links.lww.com/CM9/A483>].

In this study, we selected subjects from a Chinese population free of cardiovascular disease, diabetes, hypertension, nephropathy, and other acute and chronic diseases, therefore excluding many potential confounders. Our results are consistent with those reported by Buscemi *et al.*,^[3] who found a significant association between renal function and subclinical carotid atherosclerotic damage in people with no known renal impairment, though important kidney function parameters, such as CYSC, were not accounted for. Compared with creatinine and urea nitrogen, CYSC is a very stable indicator of the glomerular filtration rate.^[4] CYSC better reflects the changes in renal function, especially for the elderly. In fact, CYSC is not only an essential parameter of kidney function, as one of the cystatin superfamily, but imbalances between cathepsins and CYSC regulation also plays an important role in extracellular matrix remodeling, contributing to many pathological processes.^[5] In this study, CYSC has been linked to aging-related cardiovascular-renal parameters in healthy adults, suggesting that CYSC exhibits heightened sensitivity to changes in cardiovascular and glomerular function. The present investigation, underlining the role of synthetic and degradative pathways in the aging process, emphasizes that cardio-renal interaction with aging could depend partly on differential expression of some genes, leading to an imbalance among functional proteins.

There are several understandings of the sex-specific differences for our research. First of all, traditional risk factors in males may affect vascular stiffening more than females, which leads to a differential effect of CYSC on

arterial stiffness parameters, such as IMT/D. Second, CYSC has been found to participate in the pathological processes of AS, even in the early stage. An increase in coronary artery calcification by the female hormone estrogen in women is slower than that in men, indicating that CYSC plays an important role in the development of AS. Third, it is suspected that sex-specific differences may be connected with the activity of several cytokines and hormones and the differential expression of some functional proteins. Therefore, this study also suggests that sex must be considered while interpreting CYSC levels. The underlying mechanism remains to be determined. The sex-specific effects of CYSC on blood vessels verified in this study aid in the understanding of the pathological changes in atherosclerotic vascular disease.

To conclude, our study shows that in a healthy population-based cohort, eGFR, and CYSC in the normal or slightly reduced range is independently associated with age-related vascular damage. This suggests that structural arterial changes might occur early, even in the absence of overt nephropathy. Further investigation is needed to confirm and improve these findings.

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Conflicts of interest

None.

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