Serum Cystatin C and Arterial Stiffness in Middle-Aged and Elderly Adults without Chronic Kidney Disease: A Population-Based Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEG Xiaolin Huang*
BCDEG Xiaohong Jiang*
BG Long Wang
B Zhenyu Liu
B Yang Wu
B Pei Gao
A Xuegan Lian
AG Fei Hua

Department of Endocrine and Metabolic Diseases, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, P.R. China

* Xiaolin Huang and Xiaohong Jiang contributed equally
Corresponding Authors: Fei Hua, e-mail: czhuafei@vip.sina.com, Xuegan Lian, e-mail: lxgneuro@163.com
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Background: Cystatin C is a protease inhibitor that is increased in the serum of patients with chronic kidney disease (CKD) and is associated with an increased risk of developing cardiovascular disease (CVD). This study aimed to evaluate the association between serum levels of cystatin C and arterial stiffness, associated with dyslipidemia, obesity, and increased pulse pressure, in middle-aged and elderly individuals without CKD in a population in China.

Material/Methods: A cross-sectional population-based study included 1,138 patients aged ≥40 years without CKD, defined as an estimated glomerular filtration rate measured by serum creatinine (eGFR$_{SCr}$) ≥60 ml/min/1.73 m². Study participants provided clinical details, including height and weight, and blood samples for serum measurements of cystatin C and lipid profiles and completed a clinical questionnaire. Pulse pressure was calculated as the mean systolic pressure (SBP) minus the diastolic pressure (DBP). Data underwent multivariate logistic regression analysis.

Results: An increase in serum levels of cystatin C was associated with an increased risk of arterial stiffness. Each standard deviation in the increase of cystatin C resulted in a 22% increased risk of dyslipidemia, a 27% increased risk of obesity, and a 24% increased risk of increased pulse pressure, after adjusting for confounders. These associations were further confirmed in a sensitivity analysis by excluding participants with hypertension, diabetes, and patients with obstructive sleep apnea-hypopnea syndrome (OSAHS).

Conclusions: In middle-aged and elderly individuals without CKD, arterial stiffness determined by obesity, dyslipidemia and increased pulse pressure, was significantly associated with increased serum levels of cystatin C.

MeSH Keywords: Arterial Pressure • Cystatin C • Dyslipidemias • Obesity • Vascular Stiffness

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Background

Worldwide, cardiovascular disease (CVD) is a main cause of morbidity and mortality, particularly in patients with chronic kidney disease (CKD) [1,2]. Patients with CVD have arterial stiffness, which is associated with dyslipidemia, obesity, and increased pulse pressure [1]. Previous studies have shown that renal dysfunction that is evaluated by measurement of the glomerular filtration rate (GFR) is associated with an increased risk of both arterial stiffness and CKD [3,4]. Although measurement of the estimated GFR (eGFR), which is based on the measurement of serum creatinine, is the most commonly used method to evaluate renal function [5,6], the accuracy of creatinine measurements is influenced by muscle mass and body weight, which can result in less sensitivity of eGFR measurements in the elderly population with renal failure [7].

Recently, cystatin C, a cysteine protease inhibitor, has been identified as an early and sensitive marker of renal function [8]. Increased serum levels of cystatin C level are associated with medical conditions that include metabolic syndrome [9], obesity [10], and diabetes [11,12], and with lifestyle factors that include physical activity levels [13], smoking and drinking habits [13,14], and diet [15]. Although many of these medical and lifestyle factors are also associated with CVD and arterial stiffness, the role of cystatin C in CVD and arterial stiffness in individuals without CKD remains controversial. For example, reduced levels of cystatin C levels in healthy individuals has been reported to be associated with more severe atherosclerosis [16], and serum cystatin C levels were positively correlated with CVD in individuals without CKD [17].

Dyslipidemia and obesity are clinical indicators of arterial stiffness, which can be measured by pulse pressure [18]. However, few studies have investigated the association between serum cystatin C levels and dyslipidemia and pulse pressure. In 2018, Zhu et al. studied 3,348 patients from the China Antihypertensive Trial in Acute Ischemic Stroke, and measured serum cystatin C to calculate the eGFR, or $eGFR_{CysC}$ [19]. In this study, a low $eGFR_{CysC}$ was associated with poor functional outcome in patients with ischemic stroke, which was modified by low-density lipoprotein (LDL), possibly indicating a positive association between cystatin C and dyslipidemia [19]. In 2012, Peralta et al. reported the findings from the Multi-Ethnic Study of Atherosclerosis (MESA) study that compared eGFR based on serum creatinine ($eGFR_{SCr}$) in 4,853 adults and showed that an increased pulse pressure was associated with a more rapid decline in $eGFR_{CysC}$ in individuals with an $eGFR_{SCr}$ ≥60 ml/min/1.73 m² [20]. However, in 2010, Mena et al. reported that during 24-hour ambulatory blood pressure monitoring both pulse pressure and systolic blood pressure (SBP) were significantly associated with renal function, and diastolic blood pressure (DBP) was negatively correlated serum levels of cystatin C but not with GFR [21].

Therefore, this study aimed to evaluate the association between serum levels of cystatin C and arterial stiffness, associated with dyslipidemia, obesity, and increased pulse pressure, in middle-aged and elderly individuals aged ≥40 years in a population in China without CKD, defined as an $eGFR_{scr}$ ≥60 ml/min/1.73 m².

Material and Methods

Study population

This study was conducted in the communities of Zhonglou District, Changzhou, from December 2016 to December 2017. Eligible study participants had lived in Zhonglou District for more than six months, were aged ≥40 years, and were without a history of cancer. A total of 1,328 study participants were enrolled in the present study. Each study participant completed a standard clinical questionnaire and provided blood samples for biochemical analysis. Study exclusion criteria included missing data for body mass index (BMI), blood pressure, serum cystatin C, and serum lipid levels, and patients with advanced renal dysfunction who had an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m²). The number of patients who fulfilled to study inclusion criteria and were recruited into the study included 1138 study participants. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Suzhou University, and all study participants provided written informed consent to participate.

Collection of social, demographic, and clinical data

Standard questionnaires were completed by trained interviewers. Information on sociodemographic factors, lifestyle, medical history, and current drug treatment was collected through face to face interviews. Current smokers included individuals who smoked at least one cigarette per day or seven cigarettes per week for the previous six months. Current drinkers were individuals who drank alcohol at least once per week. The International Physical Activity Questionnaire short-form (IPAQ-SF) questionnaire was used to identify high or low physical activity.

Anthropometric measurements were also performed by physicians in the communities, following one week of training. Height was measured to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg, while the study participants were without shoes and wearing light clothes. The body mass index (BMI) was calculated in kg/m². After resting for at least 5 minutes, blood pressure was measured electronically with an Omron HEM-752 blood pressure monitor (Omron Company, Dalian, China) using the non-dominant arm. The participants were required to avoid alcohol, cigarettes, coffee, tea, and

exercise for at least 30 minutes before blood pressure was measured. Blood pressure measurements were performed three times every minute, with an average of three readings used for analysis. The pulse pressure was calculated as the mean systolic pressure (SBP) minus the mean diastolic pressure (DBP).

After an overnight fast for at least 10 hours, venous blood samples were collected for all study participants for biochemical measurements analysis. Serum cystatin C, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and creatinine were measured using an automated AU-5800 analyzer (Beckman Coulter, Brea, CA, USA). Fasting plasma glucose (FPG) was measured with the glucose oxidase method using an automated AU-5800 analyzer (Beckman Coulter, Brea, CA, USA).

The estimated glomerular filtration rate (eGFR) was calculated as previously described [22]. In women patients with a serum creatinine (Cr) ≤0.7 mg/dl, the eGFR was 144×(Cr/0.7)−0.329×(0.993) age; and with a serum Cr >0.7 mg/dl, the eGFR was 144×(Cr/0.7)−1.209×(0.993) age. In male patients with a serum Cr ≤0.7 mg/dl, the eGFR was 141×(Cr/0.9)−0.411×(0.993) age; and with a serum Cr >0.7 mg/dl, the eGFR was 141×(Cr/0.9)−1.209×(0.993) age.

Study groups and clinical criteria

Study participants were divided into three groups based on the tertiles or three levels of serum cystatin C, which were <0.75 mg/L, 0.75–0.86 mg/L, and 0.86 mg/L. Based on the National Cholesterol Education Program for Adult Therapy III (NCEP-ATP III), dyslipidemia was defined as TC ≥6.22 mmol/L or TG ≥2.26 mmol/L or LDL-C ≥4.14 mmol/L or HDL-C <1.04 mmol/L. A BMI ≥28 kg/m² was regarded as obesity, based on the definition from the World Health Organisation (WHO). Pulse pressure was assessed by the upper quartile of pulse pressure ≥60 mmHg. Diabetes was self-reported or diagnosed as a FPG ≥7.0 mmol/l. A SBP ≥140 mmHg and/or a DBP ≥90 mmHg or the use of antihypertensive drugs, was defined as hypertension. Screening for obstructive sleep apnea-hypopnea syndrome (OSAHS) was performed according to the Epworth Sleepiness Scale (ESS), and an ESS score ≥9 indicated OSAHS [23].

Statistical analysis

Data from the questionnaire and anthropometric measurements were analyzed using EpiData software version 3.1 (EpiData Association, Odense, Denmark). Other study data were analyzed using SAS version 9.3 software (SAS Institute Inc, Cary, NC, USA). The study participants were categorized into three groups according to serum cystatin C tertiles. Due to skewed distribution, TG and FPG were normalized using logarithmic transformation. Continuous variables and categorized variables were presented as the mean±standard deviation (SD), the median and interquartile range (IQR), and numbers with proportions, respectively. Linear regression analysis and the Cochran-Mantel-Haenszel method were used to analyze the P-values for trend across serum cystatin C tertiles for continuous and categorical variables, respectively.

Multivariate logistic regression analysis was used to assess the risk of dyslipidemia, obesity, and increased pulse pressure according to each tertile for serum cystatin C, and each standard deviation in the increase in cystatin C. Model 1 was adjusted for age and gender. Model 2 was further adjusted for other risk factors of CVD, including smoking and drinking habits, physical activity, FPG, SBP, lipid profiles, eGFR and the use of antihypertensive drugs, based on model 1.

Three further sensitivity analyses were conducted to test the validity of the results by excluding study participants with hypertension, or excluding participants with diabetes, or excluding patients with obstructive sleep apnea-hypopnea syndrome (OSAHS). P-values were calculated using the chi-squared (χ^2) test. A P-value <0.05 was considered to be statistically significant.

Results

Characteristics of the study participants

The cross-sectional population-based study included 1,138 patients aged ≥40 years without chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) measured by serum creatinine ≥60 ml/min/1.73 m². The characteristics of the study participants across the tertiles of the serum cystatin C levels, which were <0.75 mg/L, 0.75–0.86 mg/L, and 0.86 mg/L, are shown in Table 1. Patients with higher levels of serum cystatin C were older, included a higher proportion of male patients, and had higher Epworth Sleepiness Scale (ESS) score and waist circumference, but had significantly lower diastolic blood pressure (DBP), eGFR, and fasting plasma glucose (FPG) levels (all, P<0.05). Following adjusting for age and gender, the body mass index (BMI), pulse pressure, and triglyceride (TG) increased significantly, but high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were significantly reduced across the increasing serum cystatin C tertiles (P<0.05). In the study population, 40.2% of participants had dyslipidemia, 73.6% had hypertension, 19.6% were obese, 23.3% had diabetes, and 27.8% had obstructive sleep apnea-hypopnea syndrome (OSAHS) (Table 2).

Table 1. Characteristics of the study population of middle-aged and elderly adults (aged ≥40 years) without chronic kidney disease (CKD).

Variables	Serum cystatin C			P-value*
	Tertile 1	Tertile 2	Tertile 3	
Cystatin C (mg/l)	0.66±0.06	0.80±0.03	1.00±0.12	–
Age (years)	63.4±8.41	66.8±7.44	70.8±7.72	<0.0001
Male [n (%)]	87 (23.1)	126 (32.6)	191 (50.9)	<0.0001
Current smokers [n (%)]	33 (87.5)	51 (13.2)	68 (18.1)	0.09
Current drinkers [n (%)]	12 (3.2)	26 (6.7)	28 (7.5)	0.89
Higher education [n (%)]	93 (24.7)	85 (22.0)	86 (22.1)	0.07
High physical activity [n (%)]	231 (61.3)	221 (57.3)	224 (59.7)	0.28
BMI (kg/m^2)	25.0±3.3	25.5±3.4	25.8±3.6	0.004
Waist circumference (cm)	87.5±9.2	89.4±9.6	91.9±9.6	0.0007
SBP (mmHg)	132±14	134±14	136±15	0.35
DBP (mmHg)	84±9	83±8	82±9	0.03
Pulse pressure (mmHg)	48.0±11.0	51.5±12.6	53.7±13.0	0.007
TC (mmol/L)	5.23±0.92	5.15±0.99	4.99±1.03	0.12
HDL-C (mmol/L)	1.40±0.29	1.35±0.30	1.27±0.28	<0.0001
LDL-C (mmol/L)	2.82±0.67	2.72±0.68	2.62±0.69	0.004
TG (mmol/L)	1.55 (1.18–2.06)	1.66 (1.16–2.27)	1.60 (1.19–2.21)	0.02
eGFR (ml/min/1.73 m^2)	91±10	83±10	77±10	<0.0001
FPG (mmol/L)	5.60 (4.83–6.98)	5.56 (4.79–6.82)	5.52 (4.76–6.74)	0.003
Score of ESS	5.7±4.5	6.4±4.6	6.9±5.4	0.04

Data expressed as the mean±standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and numbers (percentages) for categorical variables, * P-values for trend adjusting age and gender, were calculated by the t-test for continuous variables and the chi-squared (χ^2) test for categorical variables. BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglyceride; TC – total cholesterol; FPG – fasting plasma glucose; eGFR – estimated glomerular filtration rate; ESS – Epworth sleepiness scale.

Table 2. The status of co-morbid condition of the study population.

Diseases	Status of diseases		
	Yes	No	P-value
Dyslipidemia [N (%)]	457 (40.2)	681 (59.8)	<0.0001
Hypertriglyceridemia [N (%)]	273 (24.0)	865 (76.0)	<0.0001
Hypercholesterolemia [N (%)]	149 (13.1)	989 (86.9)	<0.0001
High LDL-C [N (%)]	31 (2.7)	1107 (97.3)	<0.0001
Low HDL-C [N (%)]	174 (15.3)	964 (84.7)	<0.0001
Hypertension [N (%)]	838 (73.6)	300 (26.4)	<0.0001
Obesity [N (%)]	223 (19.6)	915 (80.4)	<0.0001
Diabetes [N (%)]	265 (23.3)	873 (76.7)	<0.0001
OSAHS [N (%)]	316 (27.8)	822 (72.2)	<0.0001

Data are expressed as numbers (percentages). P-values are calculated using the chi-squared (χ^2) test. HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; OSAHS – obstructive sleep apnea-hypopnea syndrome.
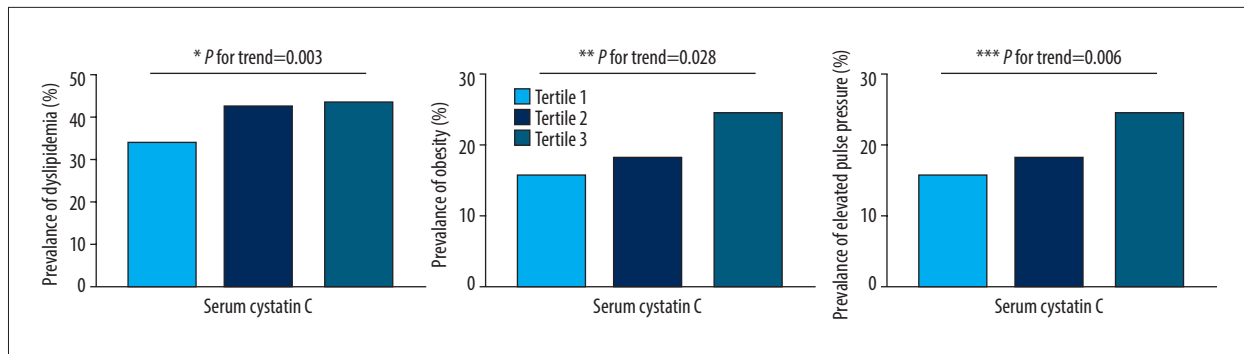
Figure 1. The prevalence of dyslipidemia, obesity, and increased pulse pressure according to serum cystatin C tertiles. * P-value adjusted for age, gender, body mass index (BMI), physical activity, smoking, and drinking status, fasting plasma glucose (FPG), systolic blood pressure (SBP), antihypertensive drugs, and estimated glomerular filtration rate (eGFR). ** P-value adjusted for age, gender, physical activity, education level, smoking, and drinking status, FPG, SBP, antihypertensive drugs, triglyceride (TG), total cholesterol (TC), and eGFR. *** P-value adjusted for age, gender, BMI, physical activity, education level, smoking, and drinking status, FPG, TG, TC, and eGFR.

Table 3. Risk of arterial stiffness according to the tertiles of serum cystatin C in middle-aged and elderly adults (aged ≥40 years) without chronic kidney disease (CKD).

Risk factors for arterial stiffness	Serum cystatin C				
	Tertile 1	Tertile 2	Tertile 3	P-value for trend	Each SD increase
Dyslipidemia					
Case/Number	128/377	165/386	164/375	–	–
Age, gender–adjusted OR	1.00 (Ref)	1.56 (1.15–2.09)	1.76 (1.27–2.43)	0.0006	1.26 (1.10–1.44)
Multivarible–adjusted OR*	1.00 (Ref)	1.53 (1.13–2.08)	1.65 (1.18–2.30)	0.003	1.22 (1.07–1.40)
Obesity					
Case/Number	60/377	71/386	92/375	–	–
Age, gender–adjusted OR	1.00 (Ref)	1.18 (0.80–1.73)	1.67 (1.13–2.48)	0.01	1.18 (1.01–1.38)
Multivarible–adjusted OR**	1.00 (Ref)	1.20 (0.80–1.81)	1.92 (1.22–2.04)	0.004	1.27 (1.05–1.53)
Increased pulse pressure					
Case/Number	78/377	120/386	149/375	–	–
Age, gender–adjusted OR	1.00 (Ref)	1.41 (1.01–1.99)	1.55 (1.08–2.23)	0.02	1.14 (0.99–1.32)
Multivariate–adjusted OR***	1.00 (Ref)	1.53 (1.07–2.20)	1.79 (1.19–2.69)	0.005	1.24 (1.05–1.46)

* The multivariate model was adjusted for age, gender, body mass index (BMI), education, physical activity, smoking, and drinking habits, fasting plasma glucose (FPG), systolic blood pressure (SBP), use of antihypertensive drugs, and estimated glomerular filtration rate (eGFR); ** P-value adjusted for age, gender, education, physical activity, smoking and drinking habits, FPG, SBP, use of antihypertensive drugs, triglyceride (TG), total cholesterol (TC), and eGFR. *** P-value adjusted for age, gender, body mass index (BMI), education, physical activity, smoking and drinking habits, FPG, TG, TC, and eGFR. SD – standard deviation; OR – odds ratio; BMI – body mass index; SBP – systolic blood pressure; TG – triglyceride; TC – total cholesterol; FPG – fasting plasma glucose; eGFR – estimated glomerular filtration rate.

The risk of arterial stiffness with the increase of serum cystatin C

The prevalence of obesity, increased pulse pressure, and dyslipidemia, which were the characteristics of arterial stiffness, increased significantly according to the cystatin C tertiles after adjusting for traditional cardiometabolic confounding factors (Figure 1). From tertile 1, tertile 2, and tertile 3 for serum cystatin C, the prevalence of dyslipidemia was 34%, 42.8%, 43.8%, obesity was 15.9%, 18.4%, 24.5%, and pulse pressure was 20.7%, 31.1% and 39.7%, respectively (all, P<0.05).
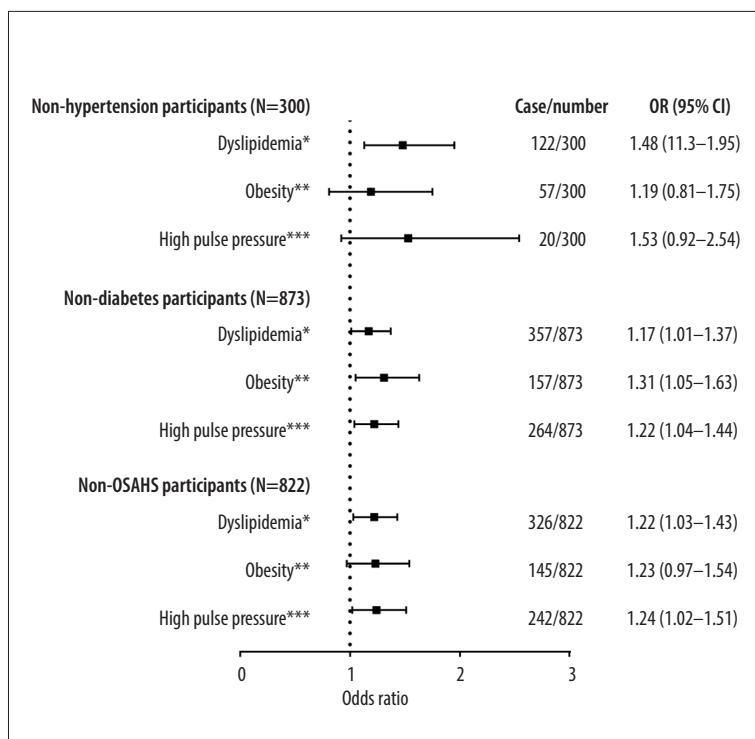
Figure 2. Sensitivity analysis of the correlation between serum cystatin C and arterial stiffness in middle-aged and elderly adults (aged ≥40 years). Odds ratios (ORs) were calculated with multiple logistic regression analysis. * Adjusted for age, gender, BMI, physical activity, education level, smoking, and drinking status, fasting plasma glucose (FPG), systolic blood pressure (SBP), antihypertensive drugs, and estimated glomerular filtration rate (eGFR). ** Adjusted for age, gender, physical activity, education level, smoking, and drinking status, FPG, SBP, antihypertensive drugs, triglyceride (TG), total cholesterol (TC), and eGFR. *** Adjusted for age, gender, BMI, physical activity, education level, smoking, and drinking status, FPG, TG, TC, and eGFR.

The relationship between serum cystatin C and dyslipidemia, obesity, and increased pulse pressure, which were the characteristics of arterial stiffness, underwent multivariate logistic regression analysis (Table 3). Compared with the lowest tertile of serum cystatin C, adjusting for multiple covariates, the second tertile was associated with a 53% increased risk of dyslipidemia and increased pulse pressure. The highest tertile of serum cystatin C was associated with a 65%, 92%, and 79% increased risk of dyslipidemia, obesity, and increased pulse pressure, respectively (all, P<0.05). Also, each standard deviation in the increase in serum cystatin C resulted in a 22% increased risk of dyslipidemia, a 27% increased risk of obesity, and a 24% increased risk of increased pulse pressure.

To examine the strength of the association between cystatin C and arterial stiffness, we further conducted three sensitivity analyses (Figure 2). Excluding participants with hypertension did not significantly change the association between serum levels of cystatin C and dyslipidemia, obesity, and increased pulse pressure, by excluding participants with diabetes and OSAHS.

Discussion

The aim of this study was to evaluate the association between serum levels of cystatin C and arterial stiffness, which was associated with dyslipidemia, obesity, and increased pulse pressure, in middle-aged and elderly individuals aged ≥40 years without chronic kidney disease (CKD) in a population

in China. In this study, CKD was defined as an estimated glomerular filtration rate measured by serum creatinine (eGFR$_{SCr}$) ≥60 ml/min/1.73 m^2. Increased serum cystatin C levels were significantly associated with an increased risk of arterial stiffness, and even in individuals with normal or mild renal impairment, measurement of serum cystatin C levels were associated with the progression of arterial stiffness in this study and this study population. To our knowledge, this is the first population-based study to show an association between serum cystatin C levels and the progression of arterial stiffness in individuals without CKD.

Previous studies have shown that renal dysfunction is a risk factor for the progression of cardiovascular disease (CVD) and that cystatin C is a more sensitive indicator than serum creatinine for renal function [24]. Also, serum cystatin C has previously been shown to be independently associated with arterial stiffness and the progression of CVD [25,26]. However, previous studies on the relationship between cystatin C and arterial stiffness, in individuals without CKD, have been limited and have shown conflicting results. Some studies demonstrated that in general population with normal renal function, serum cystatin C was an independent predictor for arterial stiffness [27–29]. In a cross-sectional study of 748 Chinese adults with an average age of 33.8 years without CKD who attended a physical examination, serum cystatin C was positively associated with brachial-ankle pulse wave velocity (PWV), which is also an indicator of arterial stiffness, independent of age, body mass index (BMI), and smoking status [27].

With the larger sample size recruited from a population in China, the findings from the present study were consistent with those of some previous studies, although different indicators of dyslipidemia, obesity, and increased pulse pressure were used [30,31]. In 2013, Yamashita et al. studied the association between serum cystatin C and arteriosclerosis in 446 patients without CKD using the carotid intima-media thickness (CIMT) and the cardio-ankle vascular index (CAVI) [32]. In this Japanese study, in women but not in men, there was a significant correlation between serum cystatin C levels and CAVI [32]. Differences in the findings from previous studies may be due to small sample size, different indices used for arterial stiffness, the specific study population, and the difference in the evaluation of eGFR evaluation. Most studies were conducted in different populations of patients with hypertension, diabetes, and obstructive sleep apnea-hypopnea syndrome (OSAHS), all of which may affect the association of cystatin C with arterial stiffness. In addition, in these studies, eGFR calculated by the Modification of Diet in Renal Disease equation is less accurate than the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in individuals with normal or mild renal dysfunction [33].

The cardiometabolic risk factors of obesity and dyslipidemia play an important role in vascular dysfunction, arterial stiffness, atherosclerosis, and CVD [34–37]. Therefore, this study investigated the impact of cystatin C on obesity and dyslipidemia as indicators of arterial stiffness in individuals without CKD. Each standard deviation in the increase in serum levels of cystatin C resulted in a 22% increased risk of dyslipidemia, and a 27% increased risk of obesity. In terms of lipid profiles, high-density lipoprotein cholesterol (HDL-C) decreased gradually with the increase of cystatin C, while triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) were negatively correlated with serum cystatin C (Table 1). After adjusting for confounding factors, the negative correlations with TG ($\beta=0.03\pm0.02$; P=0.094) and LDL-C ($\beta=-0.05\pm0.03$; P=0.07) were no longer present.

Pulse pressure was represented by the difference between the systolic and diastolic blood pressure and represented the pulsating component of blood flow, which depends on systolic ejection to distend arteries and the aorta to accommodate ejected blood and restore arterial volume [38]. Therefore, pulse pressure is considered to be a good indicator of arterial stiffness [18,39]. In the present study, there was a 24% increase in the risk of increased pulse pressure for each standard deviation of increase in serum cystatin C, suggesting the arterial stiffness, expressed as pulse pressure, was affected by the serum levels of cystatin C.

In the present study, with the increase of cystatin C, the risk of obesity, dyslipidemia, and increased pulse pressure gradually increased. However, the association could have been confounded by many of the traditional cardiovascular risk factors, including age, gender, lifestyle habits, BMI, glucose, GFR, and medication. Therefore, multivariate logistic regression analysis adjusted for these confounders, which did not alter the findings. Hypertension [40], diabetes [41], and OSAHS [42], which are closely associated with arterial stiffness and CVD, may result in bias. Sensitivity analysis excluded participants with hypertension, diabetes, and OSAHS and showed that the association between serum cystatin C and indicators of arterial stiffness remained statistically significant.

The mechanism for the association between high serum cystatin C levels and the increased risk of arterial stiffness remains unclear, but inflammation may play an important role. Previous studies have shown that serum levels of cystatin C are associated with increased levels of classical inflammatory markers, including C-reactive protein [43,44]. Increased levels of inflammatory markers, such as C-reactive protein, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), can simulate the progression of arterial stiffness through the generation of reactive oxygen species (ROS) [45,46]. Another possible explanation is that serum cystatin C as a more accurate indicator of early renal insufficiency, and indirectly affects the progression of arterial stiffness through early renal function impairment.

The main advantage of the current study was the recruitment of study participants from communities with the population studied being representative of the adult Chinese patient population. Also, sensitivity analysis excluded hypertensive and diabetic patients and patients with OSAHS, which supported the significant association between cystatin C and arterial stiffness. However, this study had several limitations. First, arterial stiffness was evaluated by obesity, dyslipidemia, and increased pulse pressure rather than aortic PWV, which is a standard measurement for arterial stiffness [47]. However, obesity, dyslipidemia, and increased pulse pressure were used as substitute indicators in previous large epidemiological studies. Second, in this study, there was a lack of information on the use of antidiabetic drugs or lipid-lowing drugs, which may have affected the findings on the association with arterial stiffness. Therefore, in future prospective studies, data on medication history should be analyzed. Third, because of the nature of cross-sectional studies, conclusions cannot be made without support from longitudinal study data. Therefore, future longitudinal studies are needed to further evaluate the role of serum cystatin C in the progression of arterial stiffness in individuals without CKD.

Conclusions

The findings from this study showed that in middle-aged and elderly adults without chronic kidney disease (CKD), serum

cystatin C had an independent positive association with arterial stiffness, which was evaluated by obesity, dyslipidemia, and increased pulse pressure. Serum cystatin C might be an early predictor of arterial stiffness in individuals without CKD. Future prospective longitudinal studies are required to demonstrate the impact of levels of serum cystatin C on the progression of arterial stiffness, arteriosclerosis, and subsequent cardiovascular disease (CVD).

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Acknowledgments

Conflict of interest

None.

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