Original Article

Serum Cystatin C Is Related to Pulse Wave Velocity Even in Subjects with Normal Serum Creatinine

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We hypothesized that serum cystatin C can be a more predictable marker of arterial stiffness than serum creatinine and creatinine-based glomerular filtration rate (GFR). The aim of this study is to evaluate whether serum cystatin C is related to arterial stiffness independently of serum creatinine in subjects for whom serum creatinine is normal. A total of 2,018 individuals (1,120 males, 898 females) were enrolled. Mean brachial-ankle pulse wave velocity (baPWV) was used as a marker of arterial stiffness and sex-specific analysis was performed. A positive relationship between baPWV and serum cystatin C ($Y=1109.0548+329.9102X$, $r^2=0.056$, $p<0.001$) was found in males. Stepwise multivariate regression analysis in males showed that age, waist circumference, heart rate, cystatin C level, triglyceride level, and fasting glucose were independent contributors to baPWV. In females, a positive relationship between baPWV and serum cystatin C ($Y=1035.7828+402.2970X$, $r^2=0.090$, $p<0.001$) was found. Stepwise multivariate regression analysis showed that age, heart rate, cystatin C level, fasting glucose and insulin level were independent contributors to baPWV. Age, heart rate, fasting glucose and serum cystatin C were the significant variables in both genders that contributed to baPWV. In conclusion, this study confirmed that serum cystatin C was related to pulse wave velocity even in subjects with normal serum creatinine. This finding suggested that cystatin C could be a more predictable marker of arterial stiffness than serum creatinine and creatinine-based GFR. (*Hypertens Res* 2008; 31: 1895–1902)

***Key Words*: cystatin C, pulse wave velocity, arterial stiffness**

Introduction

Cystatin C is a cysteine protease inhibitor and is a member of the human cysteine superfamily that has a function as a housekeeping gene with a stable production by most nucleated cells (*1*). Also, cystatin C is a nonglycosylated 13 kDa basic protein that is filtered by the glomeruli and reabsorbed and catabolized by the tubular epithelial cells, with only small amounts excreted in the urine (*2*). Because of its freely filterable size through the glomerular filtration barrier, cystatin C has been proposed as an endogenous surrogate of glomerular filtration rate (GFR) (*3*). Recently, several large epidemiological studies have shown that cystatin C is a better predictor of subjects' outcomes in coronary heart disease, acute coronary syndrome, and heart failure, independently of serum creatinine (*4–6*). Additionally, in type 1 diabetes, increasing serum cystatin C predicted progression of subclinical coronary atherosclerosis, even while adjusting for other cerebrovascular disease risk factors (*7*). Furthermore, serum cystatin C better predicted progression of subclinical coronary atherosclerosis than serum creatinine and serum creatinine–based GFR (*7*).

Arterial stiffness has been a strong independent predictor of coronary events and cardiovascular mortality in several patient groups (*8–10*). Increased arterial stiffness is one of the pathological states of vascular damage and is closely associ-

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Table 1. Baseline Characteristics of the Male Subjects According to baPWV Quartiles

Variables	Q1	Q2	Q3	Q4	*p* value
Number	280	280	282	278	
baPWV (cm/s)	1,144±84.3*,†,‡	1,300.9±35.6§,‖	1,435±43.5¶	1,731±202.1	<0.01
Age (years)	50.1±9.3†,‡	51.0±8.8‖	52.3±9.4	53.3±8.7	<0.05
Diabetes mellitus (*n* (%))	27 (9.6)	23 (8.2)	28 (9.9)	20 (7.2)	n.s.
Hypertension (*n* (%))	52 (18.6)	63 (22.5)	59 (20.9)	69 (24.8)	n.s.
Smoking (*n* (%))	62 (22.1)*,†,‡	100 (35.7)‖	112 (39.7)¶	185 (66.5)	<0.01
Waist circumference (cm)	81.4±8.6*,†,‡	83.7±7.9§,‖	85.8±7.9	85.8±8.2	<0.01
BMI	24.0±2.6†,‡	24.2±2.6	24.8±2.6	24.7±5.1	<0.01

n.s., not significant; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; Q, quartile. There were statistically significant results between the following groups: *Q1 *vs*. Q2, †Q1 *vs*. Q3, ‡Q1 *vs*. Q4, §Q2 *vs*. Q3, ‖Q2 *vs*. Q4, ¶Q3 *vs*. Q4.

Table 2. Laboratory Data for the Male Subjects According to baPWV Quartiles

Variables	Q1	Q2	Q3	Q4	*p* value
Systolic BP (mmHg)	122.3±17.0	126.0±19.0	125.0±19.0	122.3±19.3	n.s.
Diastolic BP (mmHg)	75.5±10.7*	78.1±11.2‖	77.5±11.7	75.7±11.6	<0.05
MAP (mmHg)	91.1±12.5*	94.0±13.4‖	93.3±13.7	91.2±13.6	<0.05
Heart rate (/min)	68.5±9.6*	69.1±10.1‖	68.9±10.6¶	73.2±11.8	<0.01
Pulse pressure (mmHg)	46.8±8.9	47.9±10.1	47.5±10.3	46.6±11.2	n.s.
Proteinuria (*n* (%))	8 (2.9)	16 (5.7)	15 (5.3)	22 (7.9)	n.s.
Hemoglobin (g/dL)	14.2±1.7	14.2±1.6	14.1±1.6	14.2±1.7	n.s.
Creatinine (mg/dL)	0.82±0.14*,†,‡	0.87±0.15	0.88±0.14	0.89±0.17	<0.01
GFR (mL/min/1.73 m^2)	109.6±21.7*,†,‡	102.7±20.8	100.4±20.6	100.2±22.1	<0.01
Cystatin C (mg/L)	0.84±0.16*,†,‡	0.88±0.16§,‖	0.91±0.18¶	0.94±0.19	<0.01
Uric acid (mg/dL)	5.0±1.4*,†,‡	5.5±1.4	5.5±1.4	5.6±1.4	<0.05
γ-Glutamyltransferase (IU/L)	27.0±24.3*,†,‡	37.1±49.1§,‖	46.1±50.8	49.1±67.7	<0.01
Lipid profile					
Total cholesterol (mg/dL)	193.8±30.9*,†,‡	202.6±34.2	207.8±37.4	205.9±37.1	<0.05
LDL-cholesterol (mg/dL)	119.3±27.3*,†,‡	126.2±29.0	130.8±32.6	125.6±33.6	<0.01
HDL-cholesterol (mg/dL)	56.6±13.9†,‡	55.3±13.3	53.5±12.2	52.8±14.7	<0.05
Triglyceride (mg/dL)	103.6±56.5†,‡	117.1±71.0§,‖	137.9±81.7¶	162.9±145.4	<0.01
Glucose metabolism					
Glucose (mg/dL)	87.4±13.8*,†,‡	92.0±18.5‖	93.7±16.9¶	102.4±30.0	<0.01
Insulin (μIU/mL)	4.5±3.2*,†,‡	5.3±3.2‖	5.7±3.8	6.2±4.2	<0.01
$HOMA_{IR}$	1.03±1.07*,†,‡	1.25±0.94‖	1.35±1.03¶	1.63±1.53	<0.01
C-reactive protein (mg/L)	0.13±0.30‡	0.13±0.22‖	0.16±0.28¶	0.25±0.86	<0.05

n.s., not significant; baPWV, brachial-ankle pulse wave velocity; MAP, mean arterial pressure; GFR, glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment–insulin resistance; Q, quartile. There were statistically significant results between following groups: *Q1 *vs*. Q2, †Q1 *vs*. Q3, ‡Q1 *vs*. Q4, §Q2 *vs*. Q3, ‖Q2 *vs*. Q4, ¶Q3 *vs*. Q4.

ated with atherosclerosis. Among several methods to evaluate the arterial stiffness, brachial-ankle pulse wave velocity (baPWV) is very easily measured and is a fairly reproducible method that correlates well with arterial stiffness determined by an invasive method (*11*).

In a screened cohort, increased pulse wave velocity was associated with low creatinine clearance and proteinuria (*12*). However, little data exist regarding the relationship of cystatin C to arterial stiffness in the general population. We hypothesized that serum cystatin C can be a more predictable marker of arterial stiffness than serum creatinine and creatinine-based GFR.

The aim of this study is to evaluate whether serum cystatin C is related to arterial stiffness independently of serum creatinine in subjects for whom serum creatinine is normal.

Table 3. Univariate Regression Analyses: Significant Relationship to baPWV (Male)

Variables	r^2	p value
Age	0.014	<0.001
Waist circumference	0.030	<0.001
BMI	0.012	<0.001
Heart rate	0.034	<0.001
Creatinine	0.018	<0.001
GFR	0.018	<0.001
Cystatin C	0.056	<0.001
Uric acid	0.020	<0.001
γ-Glutamyltransferase	0.020	<0.001
Total cholesterol	0.010	0.001
HDL cholesterol	0.008	0.003
Triglyceride	0.050	<0.001
Glucose	0.073	<0.001
Insulin	0.021	<0.001
$HOMA_{IR}$	0.030	<0.001
C-reactive protein	0.056	<0.001

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; GFR, glomerular filtration rate; HDL, high density lipoprotein; $HOMA_{IR}$, homeostatic model assessment–insulin resistance.

Methods

Subjects

A total of 18,572 individuals over 18 years of age participated in a 1-d health-screening program from Jan. 2006 to Dec. 2007. Of these, 2,189 individuals underwent voluntary baPWV measurement. All enrolled subjects had no history of peripheral artery disease or aortic disease. Subjects with hyperthyroidism, hypothyroidism, liver cirrhosis and abnormal serum creatinine (male, serum creatinine ≥1.5 mg/dL; female, serum creatinine ≥1.3 mg/dL) were excluded before enrollment. Also, subjects whose ankle-brachial index was more than 1.3 and less than 0.95 were excluded to ensure the accuracy of baPWV measurement before analyses. In the final analyses, a total of 2,018 individuals (1,120 males, 898 females) were enrolled. All medical and social histories and symptoms were confirmed by the consulting doctor. This study was approved by the Ethical Committee of Pusan National University Hospital.

Laboratory Data and Measurement of baPWV

Blood pressure and heart rate were measured in a seated position after resting for at least 10 min. The following laboratory data were obtained; urine protein level, hemoglobin, creatinine, cystatin C, uric acid, γ-glutamyltransferase (GGT), lipid profile, glucose, insulins, and C-reactive protein (CRP). Serum creatinine was measured by a modified Jaffe reaction (Modular D; Roche Diagnostics, Mannheim, Germany) and serum cystatin C was measured using the latex agglutination test (Modular P800; Roche Diagnostics). Homeostasis model assessment–insulin resistance ($HOMA_{IR}$) was calculated using serum levels of fasting glucose and insulin (*13*). GFR was calculated using the Abbreviated Modification of Diet in Renal Disease equation (*14*). The baPWV was measured using an automatic waveform analyzer (VP-2000; Colin Co., Komaki, Japan). All individuals were examined after resting in the supine position for at least 5 min. We used the mean baPWV (mean of the right and left baPWV) as a marker of arterial stiffness and classified the baPWV into quartiles.

Statistical Analysis

All continuous variables are expressed as mean±SD and proportions are expressed as percentage. The comparison of baPWV was performed using analysis of variance (ANOVA) with post test (Newman Keuls test of all pairs of quartiles) and χ^2 test as appropriate.

Univariate linear regression analysis and stepwise multivariate regression analysis were performed to detect significant variables that had an influence on baPWV. In this study, all data were described and analyzed according to sex. Computer software programs used for statistical analysis were MedCalc® (version 8,1,1,0) (MedCalc Software, Mariakerke, Belguim) and Prism 4® for Windows (version 4.03) (GraphPad Software, La Jolla, USA). A value of $p<0.05$ was taken to be statistically significant.

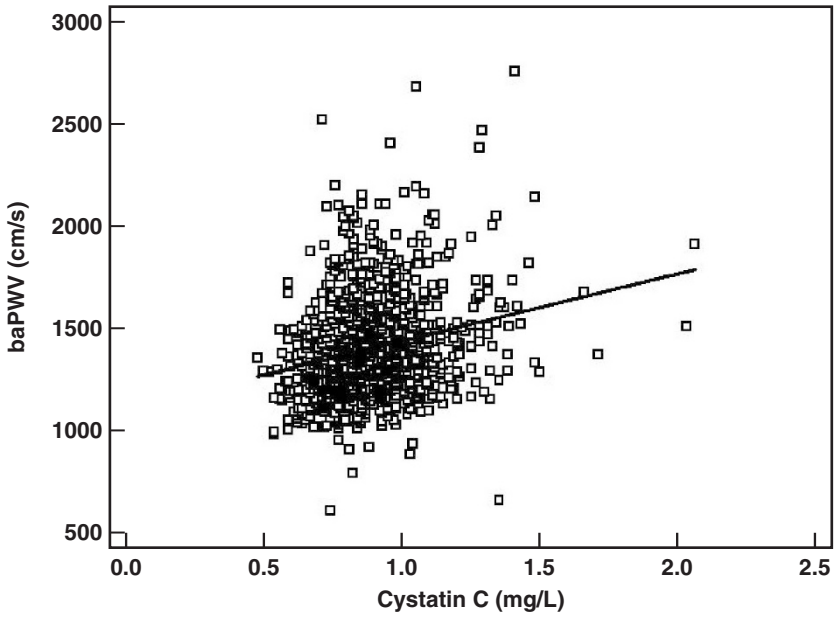

Fig. 1. *Scatter diagram with regression line of baPWV against serum cystatin C in males. Equation: baPWV = 1,109.0548 + 329.9102 × [cystatin C], $r^2 = 0.056$, $p < 0.001$.*

Table 4. Multiple Regression Analyses Showing Independent Contributions to baPWV (Male)

Independent variables	Unstandardized coefficients	β	p value
Glucose	2.167	0.191	<0.001
Cystatin C	257.478	0.185	<0.001
Heart rate	3.092	0.136	<0.001
Triglyceride	0.281	0.112	<0.001
Age	2.325	0.087	0.002
Waist circumference	1.720	0.059	0.046

Constant value: 452.130. baPWV, brachial-ankle pulse wave velocity.

Results

Results of Male Subjects

The total number of males was 1,120 and the mean age was 51.7±9.2 (22–78). Mean baPWV was 1,402±243.1 cm/s and interquartile cut-off points were 1,238.8, 1,365.8 and 1,517.0 cm/s. Table 1 shows the results of the baseline characteristics in detail. Age, proportion of smoking history, and waist circumference were higher in the 4th quartile group than in the 1st and 2nd quartiles groups.

Table 2 shows a comparison of the data according to baPWV quartiles. With increased baPWV, subjects had higher serum cystatin C, GGT, and triglycerides. In the 1st quartile group, serum creatinine, GFR, uric acid, total cholesterol, low-density lipoprotein (LDL) cholesterol, fasting glucose, insulin and $HOMA_{IR}$ were the lowest in comparison with the other quartile groups. CRP was the highest in the 4th quartile group. Univariate linear regression analysis revealed that several variables were correlated with baPWV. Table 3 shows the results for significant variables. Figure 1 shows the positive relationship between baPWV and serum cystatin C ($Y = 1{,}109.0548 + 329.9102X$, $r^2 = 0.056$, $p < 0.001$). Stepwise multivariate regression analysis showed that age, waist circumference, heart rate, serum cystatin C, serum triglycerides and fasting glucose were independent contributors to baPWV (Table 4).

Results of Female Subjects

The total number of females was 898 and mean age was 50.9±9.7 (18–84). The mean baPWV was 1,393±236.5 cm/s and the interquartile cut-off points were 1,240.0, 1,344.0 and 1,511.0 cm/s. Table 5 shows the results of the baseline characteristics in detail. All of the baseline characteristics were similar among the four quartile groups except for waist circumference. With increased baPWV, subjects had higher heart rate, serum cystatin C, serum triglycerides, fasting glucose, insulin level, and $HOMA_{IR}$ (Table 6). In the 1st quartile group, serum creatinine, GFR, and uric acid were the lowest in comparison with the other quartile groups. CRP was the highest in the 4th quartile group. Univariate linear regression analysis revealed that several variables were correlated with baPWV. However, body mass index, total cholesterol and insulin were not significantly correlated (Table 7). Figure 2 shows the positive relationship between baPWV and serum

Table 5. Baseline Characteristics of the Female Subjects According to baPWV Quartiles

Variables	Q1	Q2	Q3	Q4	*p* value
Number	225	224	225	224	
baPWV (cm/s)	1,148±88.4*,†,‡	1,291.8±30.0§,‖	1,419.4±47.6¶	1,715.0±196.7	<0.01
Age (years)	50.3±9.6	50.0±9.2	51.5±11.0	51.4±10.4	n.s.
Diabetes mellitus (*n* (%))	11 (4.9)	14 (6.2)	16 (7.1)	5 (2.2)	n.s.
Hypertension (*n* (%))	33 (14.7)	35 (15.6)	41 (18.2)	45 (20.1)	n.s.
Smoking (*n* (%))	10 (4.4)	12 (5.3)	14 (6.2)	16 (7.1)	n.s.
Waist circumference (cm)	81.7±9.0*,†,‡	83.3±8.9‖	84.4±8.5	85.8±8.1	<0.01
BMI	24.2±2.9	24.3±2.8	24.5±2.8	24.7±3.3	n.s.

n.s., not significant; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; Q, quartile. There were statistically significant results between following groups: *Q1 *vs*. Q2, †Q1 *vs*. Q3, ‡Q1 *vs*. Q4, §Q2 *vs*. Q3, ‖Q2 *vs*. Q4, ¶Q3 *vs*. Q4.

Table 6. Laboratory Data for the Female Subjects According to baPWV Quartiles

Variables	Q1	Q2	Q3	Q4	*p* value
Systolic BP (mmHg)	123.1±19.0	124.3±19.0	123.1±16.0	126.3±18.1	n.s.
Diastolic BP (mmHg)	76.1±11.6	76.5±11.5	76.1±10.0	78.1±11.1	n.s.
MAP (mmHg)	91.8±13.8	92.5±13.4	91.8±11.4	94.3±12.9	n.s.
Heart rate (/min)	67.6±10.3†,‡	68.7±12.0‖	70.2±9.5¶	72.9±11.5	<0.01
Pulse pressure (mmHg)	47.0±9.8	47.7±11.5	47.0±10.0	48.2±11.0	n.s.
Proteinuria (*n* (%))	6 (2.7)*	4 (1.8)‖	11 (4.9)¶	18 (8.0)	<0.01
Hemoglobin (g/dL)	13.5±1.7*,†,‡	14.3±1.6	14.4±1.5	14.3±1.5	<0.01
Creatinine (mg/dL)	0.82±0.14*,†,‡	0.85±0.14	0.88±0.15	0.87±0.16	<0.01
GFR (mL/min/1.73 m^2)	82.8±18.1*,†,‡	78.5±15.9	75.7±16.6	76.5±18.0	<0.01
Cystatin C (mg/L)	0.83±0.14*,†,‡	0.88±0.16‖	0.89±0.16¶	1.00±0.22	<0.01
Uric acid (mg/dL)	5.0±1.3*,†,‡	5.4±1.4	5.4±1.3	5.6±1.4	<0.01
γ-Glutamyltransferase (IU/L)	30.6±37.0†	35.9±35.3	41.8±48.7	39.3±36.1	<0.05
Lipid profile					
Total cholesterol (mg/dL)	201.9±38.2	204.2±35.1	204.8±35.7	206.9±39.0	n.s.
LDL-cholesterol (mg/dL)	125.6±34.3	127.1±29.7	126.9±31.3	128.4±35.0	n.s.
HDL-cholesterol (mg/dL)	57.3±13.6†	56.5±14.5	53.7±14.2	54.5±12.8	<0.05
Triglyceride (mg/dL)	108.7±64.3†,‡	120.2±78.8‖	140.1±91.3	142.3±89.0	<0.01
Glucose metabolism					
Glucose (mg/dL)	87.0±10.6†,‡	91.6±16.6‖	97.2±27.9	100.0±30.0	<0.01
Insulin (μIU/mL)	4.5±2.8†,‡	5.0±3.1‖	5.6±4.2¶	6.4±5.1	<0.01
$HOMA_{IR}$	1.00±0.70†,‡	1.16±0.77§,‖	1.39±1.31¶	1.67±1.72	<0.01
C-reactive protein (mg/L)	0.11±0.17‡	0.12±0.17‖	0.14±0.30	0.19±0.47	<0.01

n.s., not significant; baPWV, brachial-ankle pulse wave velocity; MAP, mean arterial pressure; GFR, glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment–insulin resistance; Q, quartile. There were statistically significant results between following groups: *Q1 *vs*. Q2, †Q1 *vs*. Q3, ‡Q1 *vs*. Q4, §Q2 *vs*. Q3, ‖Q2 *vs*. Q4, ¶Q3 *vs*. Q4.

cystatin C (Y=1,035.7828+402.2970X, r^2=0.090, p<0.001). Stepwise multivariate regression analysis showed that age, heart rate, cystatin C level, fasting glucose, and insulin level were independent contributors to baPWV (Table 8).

Age, heart rate, fasting glucose and serum cystatin C were the significant variables in both genders that contributed to baPWV.

Discussion

The remarkable finding of this study is that serum cystatin C is related to baPWV, a marker representing arterial stiffness, independently of serum creatinine and creatinine-based GFR.

Serum cystatin C has been proposed to reflect cumulative effects on GFR over time, to have less measurement variability, and to better estimate the slope in decline in GFR (*15*). Additionally, the cystatin C assay is more precise than assays

Table 7. Univariate Regression Analyses: Significant Relationship to baPWV (Female)

Variables	r^2	*p* value
Age	0.010	0.002
Waist circumference	0.029	<0.001
BMI	0.004	0.059
Heart rate	0.044	<0.001
Creatinine	0.030	<0.001
GFR	0.027	<0.001
Cystatin C	0.090	<0.001
Uric acid	0.029	<0.001
γ-Glutamyltransferase	0.006	0.020
Total cholesterol	0.004	0.054
HDL cholesterol	0.005	0.040
Triglyceride	0.018	<0.001
Glucose	0.051	<0.001
Insulin	0.001	0.190
$HOMA_{IR}$	0.049	<0.001
C-reactive protein	0.007	0.013

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; GFR, glomerular filtration rate; HDL, high density lipoprotein; $HOMA_{IR}$, homeostatic model assessment–insulin resistance.

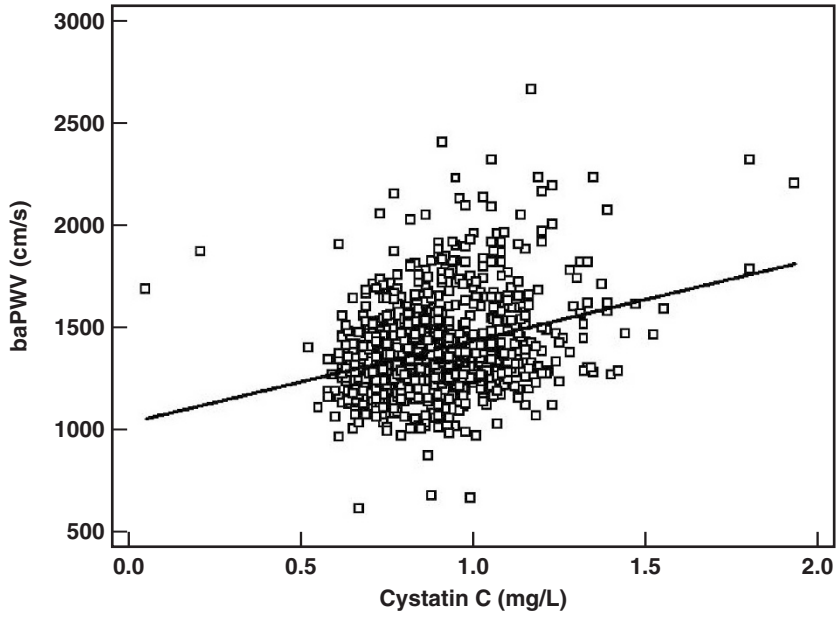

Fig. 2. *Scatter diagram with regression line of baPWV against serum cystatin C in females. Equation: baPWV = 1,035.7828 + 402.2970 × [cystatin C], $r^2 = 0.090$, $p < 0.001$.*

for serum creatinine, especially in the low range (*16*). Recently, investigators from the Cardiovascular Health Study (*17*), a community-based cohort of ambulatory elderly individuals in the US, measured cystatin C and compared cystatin C and creatinine as predictors of cardiovascular disease and mortality risk over 10 years of follow up. Consequently, cystatin C had a linear association with mortality risk, while creatinine had a J-shaped association with mortality risk. Moreover, in quintile comparison, cystatin C was associated with a significantly elevated risk of death from cardiovascular causes, myocardial infarction and stroke. Based on these results, cystatin C was a stronger predictor of the risk of death and cardiovascular events in elderly persons than creatinine. In most studies, cystatin C was used as the marker of kidney function and was superior to creatinine as a determinant of clinical outcomes. Thus, some investigators hypothesized that

Table 8. Multiple Regression Analyses Showing Independent Contributions to baPWV (Female)

Independent variables	Unstandardized coefficients	β	p value
Cystatin C	364.222	0.272	<0.001
Glucose	1.638	0.161	<0.001
Heart rate	3.396	0.158	<0.001
Age	1.783	0.076	0.014
Insulin	4.452	0.074	0.020

Constant value: 564.196. baPWV, brachial-ankle pulse wave velocity.

cystatin C may be linked to mortality by an alternative pathologic process that is distinct from its relationship to kidney function (*1*). For example, Shlipak *et al*. showed that CRP and fibrinogen levels were linearly associated with cystatin C but had a U-shaped association with creatinine and creatinine-based GFR (*18*). This relationship with inflammatory markers was identified in the present study (data not shown). One study suggested that cystatin had an atheroprotective effect in animal experiment (*19*). However, there is no pathogenetic evidence that would link cystatin C to cardiovascular mortality other than its correlation with GFR.

Several factors can affect the serum level of cystatin C, including age, male sex, smoking, higher weight, inflammatory state, liver cirrhosis, hyperthyroidism, and hypothyroidism (*20*). In the present study, subjects who had liver cirrhosis, hyperthyroidism and hypothyroidism were excluded before enrollment. Also, sex-specific analysis was performed to exclude the effect of sex on the relationship between serum level of cystatin C and baPWV.

Several lines of evidence suggest that pulse wave velocity (PWV) in patients with end-stage renal disease (ESRD) is elevated and predicts future cardiovascular disease and death (*21–23*). Furthermore, in one screened cohort, increased PWV was associated with low creatinine clearance, age, systolic blood pressure, proteinuria, fasting glucose, and cholesterol (*12*). However, in the previous study, serum creatinine and creatinine-based GFR were not independent contributors to increased baPWV (*24*). In the present study, serum cystatin C had a significant relationship with baPWV independent of other suggested contributors, but serum creatinine and creatinine-based GFR were not the independent variables in multivariate regression analysis. Elastic artery stiffness, resulting in increased PWV, could be an independent cardiovascular risk factor (*8–10*). The baPWV variable used in this study indicates the PWV of a muscular artery and could have not fully represented arterial stiffness. However, because it is well correlated with invasive method of arterial stiffness, baPWV can act as a surrogate of arterial stiffness with some limitations. Thus, the authors suggest that serum cystatin C is an independent determinant of arterial stiffness and factors related with cardiovascular outcome.

When serum cystatin C was excluded from the analysis, age, heart rate, and fasting glucose contributed to increased baPWV in both genders. Waist circumference and serum triglycerides were additional determinants in males. Also, insulin was an additional determinant in females, not in males. In initial baseline characteristics, serum triglycerides, waist circumference, and insulin levels were not different between the both sex groups (male *vs*. female: triglycerides 130.3 mg/dL *vs*. 127.8 mg/dL, $p=0.53$; waist circumference 84.2 cm *vs*. 83.8 cm, $p=0.33$; insulin 5.43 μIU/mL *vs*. 5.37 μIU/mL, $p=0.73$). These sex-specific findings could not be fully explained using the results of this study, and it was not easy to clarify the relationship between cause and result. In our opinion, the difference in exposure to hormones such as estrogen may leads to the difference of vascular protective mechanisms. The difference in vascular effects according to sex may lead to different statistical results.

In summary, this study confirmed that serum cystatin C is related to PWV even in subjects with normal serum creatinine. This finding suggested that cystatin C could be a more predictable marker of the arterial stiffness than serum creatinine and creatinine-based GFR.

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