Kidney International, Vol. 65 (2004), pp. 1416–1421

Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement

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Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement.

Background. It is well known that serum creatinine may be used as a marker of renal function only if taking into account factors that influence creatinine production, such as age, gender, and weight. Serum cystatin C has been proposed as a potentially superior marker than serum creatinine, because serum cystatin C level is believed to be produced at a constant rate and not to be affected by such factors. However, there are limited data on factors that may influence serum cystatin C levels, and there are limited data comparing cystatin C-based estimates of renal function with creatinine-based estimates that adjust for such factors, especially in individuals with normal, or mildly reduced, renal function.

Methods. This was a cross-sectional study of 8058 inhabitants of the city of Groningen, The Netherlands, 28 to 75 years of age. Serum cystatin C and serum creatinine levels were measured, and creatinine clearance was determined from the average of two separate 24-hour urine collections. We performed multivariate analyses to identify factors independently associated with serum cystatin C levels after adjusting for creatinine clearance. Then, partial Spearman correlations were obtained after adjusting for factors that may influence serum cystatin C and creatinine levels. We also compared the goodness-of-fit (R^2) of different multivariate linear regression models including serum cystatin C level and serum creatinine level for the outcome of creatinine clearance.

Results. Older age, male gender, greater weight, greater height, current cigarette smoking, and higher serum C-reactive protein (CRP) levels were independently associated with higher serum cystatin C levels after adjusting for creatinine clearance. After adjusting for age, weight, and gender, the partial Spearman correlations between creatinine and, respectively, serum cystatin C level and serum creatinine level were -0.29 ($P < 0.001$) and -0.42 ($P < 0.001$), respectively. The R^2 values for serum cystatin C level and serum creatinine level adjusted for age, weight, and gender were 0.38 and 0.42, respectively. The addition of cigarette smoking and serum CRP levels did not improve the R^2 value for the multivariate serum cystatin C-based model.

Conclusion. Serum cystatin C appears to be influenced by factors other than renal function alone. In addition, we found no evidence that multivariate serum cystatin C–based estimates of renal function are superior to multivariate serum creatinine-based estimates.

Key words: serum creatinine, serum cystatin C, creatinine clearance, renal function measurement, PREVEND.

Received for publication September 11, 2003
and in revised form October 30, 2003
Accepted for publication November 12, 2003

Serum creatinine level is commonly used to estimate renal function. Serum creatinine level, though, is not only determined by its renal excretion, but also by its production in muscular tissue, which is dependent on age, weight, and gender. Therefore, when using serum creatinine level to estimate renal function, one needs to adjust for these factors. Thus, these parameters are incorporated into the Cockcroft-Gault formula for estimating renal function [1].

Serum cystatin C level is another marker of renal function that has been proposed as potentially superior to serum creatinine level for estimating renal function, because it is thought to be produced at a constant rate by most nucleated cells [2]. Moreover, cystatin C production has been reported to be not affected by age [3, 4], gender [3, 5], or muscle mass [6]. Cystatin C is freely filtered at the level of the glomerulus and virtually all is reabsorbed and metabolized by the proximal tubular cells [7]. Therefore, assuming constant cellular production, serum cystatin C level has the potential to be an excellent surrogate marker of glomerular filtration rate (GFR).

A recent meta-analysis concluded that serum cystatin C level is a superior marker of renal function compared with serum creatinine level [8]. However, this meta-analysis did not adjust for other factors that may affect serum creatinine and serum cystatin C levels by influencing the production of the marker. There are a few small studies

comparing the performance of serum cystatin C level and serum creatinine level for estimating renal function that take into account such factors, but these studies have had conflicting results [9–14]. Thus, to address this paucity of information, we analyzed the performance characteristics of serum cystatin C and creatinine levels for estimating measured creatinine clearance utilizing data collected in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort, a population-based sample of 8592 individuals from Groningen, The Netherlands, designed to study the impact albuminuria on cardiovascular and renal diseases in the general population. We incorporated clinical and laboratory information into our estimates of creatinine clearance in order to improve the correlations and goodness-of-fit of serum cystatin C and serum creatinine levels for estimating measured creatinine clearance. We specifically addressed whether factors that are known to influence serum creatinine-based estimates of creatinine clearance, such as age, gender, and weight, as well as other cardiovascular risk factors, such as C-reactive protein (CRP) level and smoking, could improve the predictive ability of serum cystatin C level to estimate creatinine clearance.

METHODS

Study population

We utilized data from the PREVEND cohort. Details of this study have been presented elsewhere [15]. In 1997 and 1998, all inhabitants aged 28 to 75 years of the city of Groningen, The Netherlands, were asked to answer a short questionnaire and send in a morning urine sample. Pregnancy and insulin-requiring diabetes were exclusion criteria. We received a response from 40,856 individuals. We selected all individuals with a urine albumin concentration ≥10 mg/L ($N = 7768$) and a random sample of 3395 individuals with a urine albumin concentration <10 mg/L. These individuals were invited to an outpatient medical clinic for further screening. All participants who came for further screening completed a more detailed questionnaire that asked about demographic and medical information, and fasting blood samples were obtained to measure serum cystatin C level, serum creatinine level, and other laboratory parameters. Anthropometric information was recorded, blood pressure was measured during 10 minutes on two separate days and two consecutive 24-hour urine collections were obtained to measure creatinine clearance. The screening program was completed by 8592 individuals. For the present study we excluded 534 individuals who were missing information on serum cystatin C level, serum creatinine level, or creatinine clearance. This left a total of 8058 individuals for our analyses. Less than 5% of individuals (425/8592) in the total cohort reported a race other than Caucasian.

Measurement of serum cystatin C, serum creatinine, and creatinine clearance

Serum cystatin C level was measured by nephelometry (BN II N) (Dade Behring Diagnostic, Marburg, Germany) and reported as milligrams per liter. The intra- and interassay coefficients of variation were <4.1% and <3.3%, respectively. Serum creatinine level was measured in one laboratory using an automated enzymatic method (Eastman Kodak, Rochester, NY, USA). The intra- and interassay variation coefficient of serum creatinine were respectively 0.9% and 1.1%. For urinary creatinine the coefficients were respectively 0.9% and 2.9%. Each 24-hour urine creatinine clearance was calculated by multiplying the mean of day 1 and 2 urine creatinine concentration by the 24-hour urine volume divided by serum creatinine. For all analyses, we utilized the mean of the two creatinine clearance measurements. The units for creatinine clearance are mL/min.

Measurement of other factors

Weight was measured at the outpatient clinic to the nearest 0.5 kg with a Seca balance scale (Seca Vogel & Halke GmbH & Co, Hamburg, Germany). Height was measured to the nearest 0.5 cm. Smoking was assessed by questionnaire. Diabetes was defined as a fasting glucose level of ≥7.0 mmol/L, a nonfasting glucose level ≥11.1 mmol/L, or the use of oral antidiabetic medication. Hyperlipidemia was defined as follows: (*1*) a serum cholesterol of ≥6.5 mmol/L; (*2*) a serum cholesterol ≥5.0 mmol/L if an individual had a prior myocardial infarction; or (*3*) the use of lipid-lowering medication. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg or the use of lipid-lowering medication. CRP was measured by nephelometry with a threshold of 0.175 mg/L and intra- and interassay coefficients of <4.4% and 5.7% respectively. An elevated CRP level was defined as ≥3 mg/L [16].

Urinary albumin concentration was determined by nephelometry with a threshold of 2.3 mg/L and intra- and interassay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic). For the calculation of the prevalence of elevated urinary albumin excretion (UAE), we excluded subjects with leucocyturia and erythrocyturia.

Obesity was defined as a body mass index (BMI) ≥30 kg/m^2.

Statistical analysis

For continuous variables, the mean, standard deviation and 5% to 95% range were calculated. For categoric variables, we examined the percentage of individuals in each category. We identified factors associated with serum

cystatin C levels using multivariate linear regression analyses with the following prespecified covariates: creatinine clearance (continuous), age (years), gender (male or female), weight (kg), height (m), current smoking (yes or no), diabetes (yes or no), hyperlipidemia (yes or no), hypertension (yes or no), and elevated CRP level. Since serum cystatin C levels were not normally distributed on univariate analysis, the natural logarithm of serum cystatin C level was used for these analyses. We performed similar analyses using the natural logarithm of serum creatinine level.

Next, we examined the Spearman correlations between both serum cystatin C and serum creatinine levels and creatinine clearance, and we examined partial Spearman correlations adjusted for age, gender, weight, height, CRP level, and smoking status. We repeated these analyses excluding individuals whose two 24-hour creatinine clearance measurements differed by more than 20%.

After assessing the normality assumption for creatinine clearance, we performed linear regression to examine the R^2 values of different models to predict creatinine clearance. The R^2 value is defined as the regression sum of squares divided by the total sum of squares, and can be thought of the proportion of the variance of the dependent variable explained by the independent variables. We examined the R^2 values for both serum cystatin C level and serum creatinine level individually, and we examined different multivariate models that included serum cystatin C and serum creatinine level. We also examined multivariate models of creatinine clearance excluding individuals whose two 24-hour creatinine clearance values differed by more than 20%.

Finally, we utilized multivariate receiver-operating characteristic (ROC) analyses to examine the ability of serum cystatin C and serum creatinine levels to predict a creatinine clearance of <60 mL/min or <90 mL/min. Using these data, we were able to compare the areas under the curve (AUC) for these different estimates of renal function.

All analyses were performed using SAS Statistical Software version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the participants are presented in Table 1. Tables 2 and 3 present participant characteristics stratified by serum cystatin C and serum creatinine quintiles, respectively. On multivariate linear regression analysis, also adjusting for creatinine clearance, older age, male gender, greater weight, greater height, current cigarette smoking, and a high CRP level were each independently positively associated with serum cystatin C levels. Hyperlipidemia, hypertension, and diabetes were not significantly associated with serum cystatin C levels. As expected, male gender, greater weight, and greater height, but similarly also hyperlipidemia and hypertension were each independently positively associated with serum creatinine levels after adjusting for creatinine clearance. Similarly older age, but also diabetes and cigarette smoking were each independently negatively associated with serum creatinine levels. CRP level was not significantly associated with serum creatinine level.

Table 1. Demographic and laboratory data for individuals in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort with percentages, means, standard deviations, and 5% to 95% ranges (total $N = 8058$)

Age *years*	49 ± 13 (range 31–71)
Male %	50
Serum cystatin C *mg/L*	0.80 ± 0.21 (range 0.57–1.12)
Serum creatinine *mg/dL*	0.95 ± 0.22 (range 0.72–1.24)
Creatinine clearance *mL/min*	102 ± 27 (range 63–148)
Weight *kg*	78 ± 14 (range 58–104)
Body mass index (≥30 kg/m^2) %	15
C-reactive protein (≥3 mg/L) %	25
Current smoker %	37
Diabetes %	4
Hyperlipidemia %	25
Hypertension %	32
Urinary albumin excretion (≥30 mg/day) %	14

The mean, standard deviation, and 95% range are presented for continuous variables, and percentages are reported for categorical variables.
To convert mg/dL to umol/L multiply by 88.402.

Serum cystatin C and serum creatinine level were positively correlated ($r = 0.44$, $P < 0.001$). Serum cystatin C level alone ($r = -0.23$, $P < 0.001$) was better correlated with creatinine clearance than serum creatinine level alone ($r = -0.08$, $P < 0.001$). Serum cystatin C level was highly correlated with age, moderately correlated with weight and serum CRP level and weakly correlated with height (Table 4). Serum creatinine level was highly correlated with weight and height, moderately correlated with age and weakly correlated with serum CRP level (Table 4). When we examined the partial correlations between both serum cystatin C level and serum creatinine level with creatinine clearance adjusted for age, weight, and gender, the correlations for serum cystatin C level and serum creatinine level each improved; however, serum creatinine level ($r = -0.42$, $P < 0.001$) was better correlated with creatinine clearance than serum cystatin C level ($r = -0.29$, $P < 0.001$). When we added CRP level and current cigarette smoking (the additional factors independently associated with serum cystatin C levels), the correlation between serum cystatin C level and creatinine clearance did not change.

The R^2 values for serum cystatin C level and serum creatinine level alone were both low (Table 5). The addition of age, weight, and gender increased the R^2 value for both serum cystatin C level and serum creatinine level (Table 5). The addition of height, CRP level, cigarette smoking, diabetes, hypertension, and hypercholesterolemia to the models including age, weight, and

Table 2. Demographic and laboratory data for individuals in the of Renal and Vascular End-Stage Disease (PREVEND) cohort stratified by cystatin C quintile (total $N = 8058$)

	Quintiles of cystatin C				
	1	2	3	4	5
Serum cystatin C level *mg/L*	0.58 ± 0.10	0.71 ± 0.02	0.78 ± 0.02	0.86 ± 0.03	1.08 ± 0.28
Minimum	0.05	0.67	0.75	0.82	0.91
Maximun	0.66	0.74	0.81	0.90	6.15
Age *years*	43 ± 10	45 ± 11	48 ± 12	51 ± 13	58 ± 12
Male %	31	44	52	59	64
Weight *kg*	73 ± 14	77 ± 14	79 ± 14	81 ± 14	82 ± 14
Body mass index (≥30 kg/m^2) %	10	13	16	17	20
C-reactive protein (≥3 mg/L) %	17	21	22	26	38
Current smoker %	28	35	38	43	43
Diabetes %	3	3	3	4	6
Hyperlipidemia %	17	21	25	30	36
Hypertension %	19	23	29	35	53
Urinary albumin exretion (≥30 mg/day) %	10	9	13	14	25
Serum creatinine *mg/dL*	0.86 ± 0.13	0.90 ± 0.13	0.93 ± 0.13	0.97 ± 0.14	1.09 ± 0.39
Measured creatinine clearance *mL/min*	107 ± 26	107 ± 26	106 ± 26	102 ± 25	89 ± 26

The mean and standard deviation are presented for continuous variables, and percentages are reported for categorical variables.
To convert mg/dL to umol/L multiply by 88.402.

Table 3. Demographic and laboratory data for individuals in the of Renal and Vascular End-Stage Disease (PREVEND) cohort stratified by creatinine quintile (total $N = 8058$)

	Quintiles of creatinine				
	1	2	3	4	5
Serum creatinine *mg/dL*	0.74 ± 0.05	0.85 ± 0.02	0.93 ± 0.02	1.02 ± 0.03	1.21 ± 0.35
Minimum	0.49	0.81	0.89	0.97	1.07
Maximum	0.80	0.88	0.96	1.06	11.8
Age *years*	47 ± 12	47 ± 12	49 ± 13	50 ± 13	54 ± 13
Male %	10	25	49	73	90
Weight *kg*	72 ± 14	74 ± 14	78 ± 14	82 ± 13	85 ± 13
Body mass index (≥30 kg/m^2) %	17	14	14	16	17
C-reactive protein (≥3 mg/L) %	28	24	23	23	26
Current smoker %	42	41	38	35	32
Diabetes %	4	3	3	3	5
Hyperlipidemia %	22	21	25	28	33
Hypertension %	25	24	29	32	48
Urinary albumin exretion (≥30 mg/day) %	11	9	12	13	25
Cystatin C *mg/L*	0.71 ± 0.15	0.75 ± 0.16	0.79 ± 0.18	0.82 ± 0.18	0.93 ± 0.30
Measured creatinine clearance *mL/min*	105 ± 26	102 ± 26	103 ± 27	106 ± 27	96 ± 27

The mean and standard deviation are presented for continuous variables, and percentages are reported for categorical variables.
To convert mg/dL to umol/L multiply by 88.402.

Table 4. Spearman correlations between cystatin C, creatinine, age, weight, height, and C-reactive protein level (total $N = 8058$)

	Age *years*	Weight *kg*	Height *m*	C-reactive protein *mg/L*
Cystatin C *mg/L*	0.41	0.22	0.08	0.26
Creatinine *mg/dL*	0.18	0.37	0.41	0.03

All P values for reported correlation <0.001.

Table 5. R^2 values for different models to estimate 24-hour creatinine clearance using serum cystatin C and creatinine (total $N = 8058$)

	Cystatin C	Creatinine
Alone	0.06	0.03
+ age	0.10	0.09
+ age and weight	0.35	0.35
+ age, weight, and gender	0.38	0.42

gender, had no substantial impact on the R^2 values for serum cystatin C level or serum creatinine level. When we limited the analyses to individuals whose two measured creatinine clearance values differed by ≤20%, the R^2 adjusted for age, weight, and gender improved from 0.38 to 0.46 for serum cystatin C level, and from 0.42 to 0.56 for serum creatinine level.

When we constructed ROC curves, the AUC values were 0.71 for serum cystatin C level alone and 0.66 for serum creatinine level alone for predicting a measured creatinine clearance < 60 mL/min. The AUC for serum cystatin C level adjusted for age, weight, and gender was 0.79, and the addition of CRP level and smoking status did not improve the AUC. The AUC for serum creatinine level adjusting for age, weight, and gender was 0.81. The

AUC values were similar when we examined the prediction of a measured creatinine clearance <90 mL/min.

DISCUSSION

In a general population sample, factors related to serum cystatin C production and/or catabolism might have more influence on serum cystatin C levels than GFR. Therefore, it is important to note that not only older age, male gender, and greater weight, and height but also current cigarette smoking and higher CRP levels were independently associated with higher serum cystatin C levels after adjusting for creatinine clearance. These associations are thus not due to the fact that factors as obesity [17–20], smoking [21, 22] and CRP [23, 24] are related to renal function. They, in contrast, indicate that these factors may influence cystatin C independent of their effects on renal function.

The association between age and serum cystatin C levels contrasts with some reports [3, 4], although other studies have shown that serum cystatin C levels are higher in older individuals [25, 26]. The observed associations between male gender, greater weight and smoking and higher serum cystatin C levels are consistent with the observations of Galteau et al [26], but that study did not adjust for level of renal function. Wasén et al [27] studied elderly subjects and concluded that (cardiovascular) risk factors are associated with both cystatin C and serum creatinine although their R^2 was higher for cystatin C. Again they did not adjust for level of renal function. The univariate association between higher serum cystatin C levels and higher CRP levels may be partially explained by the fact that obesity [28–31] and smoking [32, 33] are both associated with higher CRP levels. However, the association between serum cystatin C level and CRP remained significant after adjusting for other factors, so serum cystatin C may also be a biomarker of inflammation [34–36]. Thus, contrary to many reports, serum cystatin C levels do appear to be influenced by multiple factors other than renal function.

We found that serum cystatin C level alone was a better predictor of creatinine clearance than serum creatinine level, as assessed by the correlation with creatinine clearance, the goodness-of-fit statistic (R^2), and the AUC of the ROC curve. However, when we incorporated clinical information such as age, weight, and gender into our models, serum cystatin C level did not perform better than serum creatinine level for predicting creatinine clearance. Our data also show that taking into account age, weight, and gender improved the predictive performance of serum cystatin C level, albeit to a smaller extent than serum creatinine level. Thus, caution must be used when interpreting cystatin C levels alone.

The observation that serum cystatin C level alone is superior to serum creatinine level alone for predicting creatinine clearance is not surprising, given the published literature on this topic. However, the correlations we observed were smaller than the published literature in individuals with chronic kidney disease. For example, Coll et al [9] observed a correlation of 0.77 between 1/cystatin C and iothalamate clearance and 0.73 between 1/serum creatinine and iothalamate clearance. In this same study, the authors reported a correlation of 0.74 between 24-hour creatinine clearance and iothalamate clearance. Assuming the correlations between serum cystatin C and serum creatinine and creatinine clearance would be slightly less than the correlation between these biomarkers and GFR, these correlations are still much higher than what we observed. Other authors have reported that the correlations between both serum cystatin C and serum creatinine level and GFR are much less in individuals with a normal GFR [12, 13], which may explain why the correlations we observed are lower than some of the reported literature on this topic.

The most important limitation of our analyses is that we used 24-hour creatinine clearance to estimate renal function instead of directly measuring GFR. It would be logistically difficult to obtain true GFR measurements in such a large population. We, however, feel that the use of creatinine clearance as the golden standard for renal function measurement does not diminish the certainty of our conclusions regarding imperfections of serum cystatin C versus serum creatinine as measure of renal function, as both the correlation between serum cystatin C and creatinine clearance and between serum creatinine and creatinine clearance improved comparably by the exclusion of the outliers. This limitation is counterbalanced by the large population and our ability to examine a large number of factors that could potentially influence serum cystatin C and serum creatinine levels. Another potential limitation is generalizability. This population was almost exclusively Caucasian, so these results may not be generalized to other racial groups. It is also possible that we may have overlooked some factors that may influence serum cystatin C levels, because the literature on this topic is limited.

These results suggest that serum cystatin C level should not be used to estimate renal function unless one accounts for other factors that may influence serum cystatin C levels. In addition, serum cystatin C-based estimates of renal function that incorporate other factors that may influence serum cystatin C level, such as age, weight, gender, CRP level, and smoking, do not appear to be superior to serum creatinine-based estimates of renal function.

ACKNOWLEDGMENTS

We thank J.J. Duker and J.W.J.T. van der Wal-Hanewald for their assistance with the laboratory assays.

This work was supported by grant E013 of the Dutch Kidney Foundation, Bussum, The Netherlands, grants T32DK07791 and DK52866

from the National Institutes of Health, United States, and Dade Behring supplied laboratory equipment and analytes.

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