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Plasma Cystatin C Concentration Reflects the Severity of Coronary Artery Disease in Patients Without Chronic Kidney Disease

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Background: This study examines whether the serum concentration of cystatin C (Cys C) correlates with the severity of coronary artery disease (CAD) and whether it provides additional information on the risk for CAD in patients without chronic kidney disease (CKD) estimated by the creatinine-based glomerular filtration rate (GFR).

Methods and Results: The relationship between serum Cys C and the severity of CAD in 526 patients was investigated. Based on GFR, patients were divided into those with and without CKD. The relationship of serum Cys C with the severity of CAD was examined. Serum Cys C was closely correlated with GFR in all cases and in CKD patients, but not in non-CKD patients. The average number of stenotic coronary arteries was significantly higher in the quartiles of higher concentration of Cys C as well as in those of GFR. In 348 patients (66%) the GFR was $\geq 60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$. Those patients with increased Cys C (>0.90 mg/L, 143 patients) had a significantly larger number of stenotic coronary arteries than those patients with normal Cys C.

Conclusions: Among patients considered to be at low risk based on the estimated GFR using serum creatinine, those with high concentrations of Cys C could have severe CAD. Besides CKD, Cys C might serve as a marker of CAD severity. (*Circ J* 2010; **74:** 2441–2447)

Key Words: Chronic kidney disease; Coronary artery disease; Glomerular filtration rate; Renal function

It has been widely recognized that cardiovascular events frequently occur in patients with chronic kidney disease (CKD), especially in those with stage 5 CKD.[1–4] However, recent studies have found that cardiovascular disease was not rare in patients with a milder decline of renal function, that is, in stage 3 CKD.[5–7] While the estimated glomerular filtration rate (GFR), calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation based on the level of serum creatinine (SCr), is frequently used in the diagnosis of CKD,[8] some studies have indicated that the level of SCr greatly depends on the patient muscle mass and that it varies very little in patients with mild renal dysfunction.[9–11] Cystatin C (Cys C) is a low molecular weight protein produced by all nucleated cells at a constant rate regardless of variations of the intracellular and extracellular environment, and acts as a cysteine protease inhibitor. Cys C does not form a complex with other serum proteins in blood, and is filtered by the renal glomeruli to be reabsorbed and degraded in the proximal tubules. Moreover, some reports have pointed out that the plasma concentration of Cys C does not depend on patient size, shows a strong negative correlation with GFR, and is a better marker of especially mild renal dysfunction than SCr.[12,13] In this study, we examined whether the concentration of Cys C could serve to predict the severity of coronary artery disease (CAD) in patients with CAD considered not to have CKD in terms of the GFR estimated from the concentration of SCr.

Methods

The subjects were consecutive 526 patients (67±10 [SD] years old) who underwent coronary angiography (CAG) in our department under the suspected diagnosis of CAD between October 2005 and July 2008. Patients with stage 5 CKD were excluded. Blood samples were collected before CAG from the antecubital vein of the patients who were resting in the supine position. The serum concentration of Cys C was determined by fluorescent enzyme immunoassay (ST AIA-PACK Cystatin C; TOSOH Corporation, Tokyo, Japan). The plasma level of BNP was also determined by fluorescent enzyme

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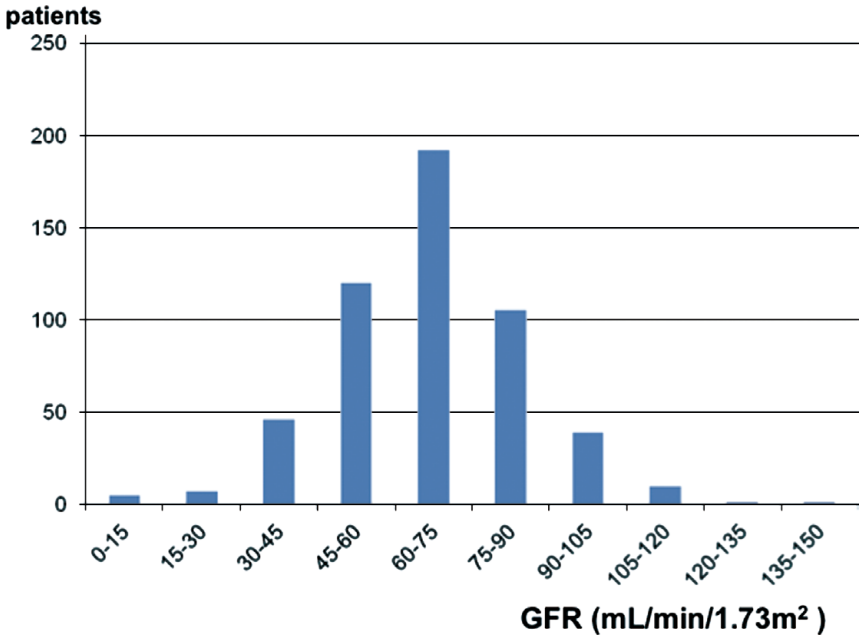

Figure 1. Distribution of patients by the glomerular filtration rate (GFR).

Table 1. Clinical Background of CKD and Non-CKD Patients Classified According to the Estimated GFR

	Total (GFR)	Non-CKD $-60\,ml\cdot min^{-1}\cdot 1.73\,m^{-2}$	CKD $60>ml\cdot min^{-1}\cdot 1.73\,m^{-2}$	P value
N	526	348	178	
Age (years old)	67.1±9.5	65.4±9.5	70.3±8.8	<0.0001
Sex (M/F)	409/117	263/85	146/32	0.093
Hypertension (%)	89.7	85.9	97.2	<0.0001
Dyslipidemia (%)	73.8	73.6	74.2	0.884
Diabetes mellitus (%)	43.9	37.4	56.7	<0.0001
Smoking habit (%)	43.7	42.5	46.1	0.439
Prior MI (%)	13.5	11.8	16.9	0.080
HbA_{1c} (%)	6.05±1.18	5.96±1.12	6.23±1.27	0.011
Hb (g/dl)	13.4±1.6	13.7±1.4	12.8±1.7	<0.0001
SCr (mg/dl)	0.92±0.37	0.76±0.14	1.23±0.47	<0.0001
Cys C (mg/L)	1.05±0.47	0.89±0.15	1.35±0.68	<0.0001
GFR $(ml\cdot min^{-1}\cdot 1.73\,m^{-2})$	66.3±18.2	75.9±13.0	47.5±10.8	<0.0001
BNP (pg/ml)	64.1±139.6	43.7±59.3	103.8±220.2	<0.0001
LVEF (%)	57.8±11.7	57.8±11.8	57.6±11.7	0.874
Number of stenotic arteries				
0	148	113	35	0.0016
1	125	88	37	
2	103	61	42	
3	150	86	64	

Data are expressed as the mean±SD or percentage.
CKD, chronic kidney disease; GFR, glomerular filtration rate; MI, myocardial infarction; Hb, hemoglobin; SCr, serum creatinine; Cys C, cystatin C; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

immunoassay. The values of other laboratory parameters were obtained from samples assayed in an autoanalyzer. Serum creatinine was determined by an enzymatic method. GFR was estimated using the MDRD equation, applying coefficients corrected for the Japanese population based on the concentration of SCr [GFR $(ml\cdot min^{-1}\cdot 1.73\,m^{-2}) = 194\times SCr^{1.094}\times Age^{-0.287}$ (×0.739, if female)].[14] Patients with a GFR <60 $ml\cdot min^{-1}\cdot 1.73\,m^{-2}$ were diagnosed as having CKD. Left ventricular ejection fraction (LVEF) was measured by echocardiography [(end-diastolic volume−end-systolic volume)/end-diastolic volume]. The cardiovascular risk was assessed in terms of hypertension, diabetes mellitus, and dyslipidemia. Patients with hypertension were assessed as being at risk if their blood pressure was ≥140/90 mmHg or if they had a history of antihypertensive drug use. Patients with diabetes mellitus were assessed as being at risk if their fasting glucose

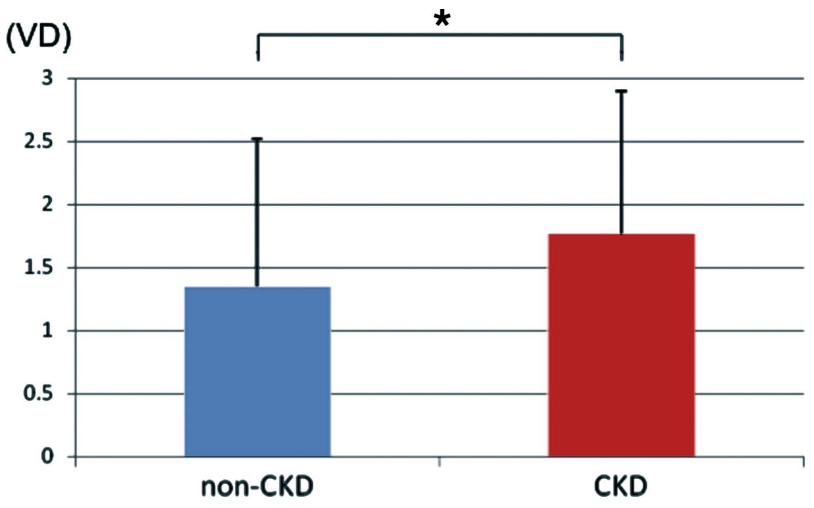

Figure 2. Mean number of stenotic coronary arteries in patients with chronic kidney disease (CKD) and those without CKD. *P<0.001 vs non CKD. VD, vessel disease.

level was ≥126 mg/dl or if they had a history of hypoglycemic drug or insulin use. Patients with dyslipidemia were assessed as being at risk if their LDL cholesterol was ≥140 mg/dl or their HDL cholesterol was ≤40 mg/dl, or if they were taking a hypolipidemic drug.

The results of CAG were evaluated by at least 2 operators. The degree of coronary stenosis was assessed in the direction that showed the most severe stenosis according to the American Heart Association standards.[15] Patients were assessed as having significant coronary stenosis if their stenosis was ≥51%. The left anterior descending artery, left circumflex artery, and right coronary artery were examined to evaluate the number of stenotic coronary arteries as 0 to 3-vessel disease (VD). If the left main trunk was involved, this was evaluated as a 2-VD by itself. The relationship between CKD and the number of stenotic coronary arteries was analyzed using the average number of stenotic arteries to assess the severity of CAD. The relationship between the serum concentration of Cys C and the severity of CAD was also analyzed in non-CKD patients.

This study is a retrospective study and was carried out after we obtained approval from the Ethical Review Board of our institution (No. 2252).

Statistical Analysis

The values of laboratory parameters are presented as the mean±SD. A Student's t-test was used for comparisons between the 2 groups and Dunnett's multiple comparison of means was used for multi-group comparison after analysis of variance (ANOVA). The correlation coefficient was obtained by the method of least squares. Distribution of stenotic vessel numbers was tested by the chi-square test. The results were considered statistically significant at P<0.05. SPSS version 17.0 (Chicago, IL, USA) was used to carry out the statistical analysis.

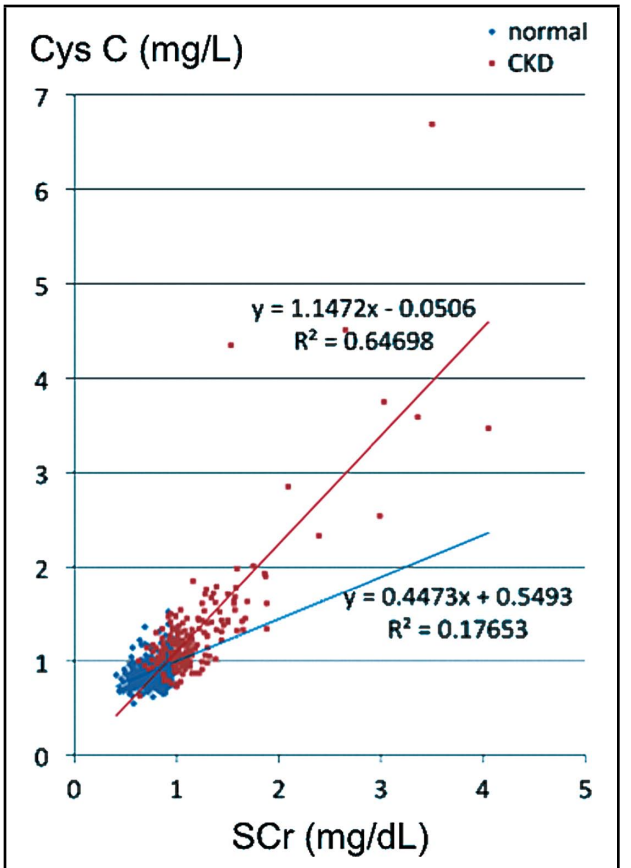

Figure 3. Correlation between SCr and serum Cys C in the whole population as well as in the CKD group and the non-CKD group. SCr, serum creatinine; Cys C, cystatin C; CKD, chronic kidney disease.

Results

The GFR was normally distributed (Figure 1). The average GFR was 66.3±18.2 ml·min^{-1}·1.73 m^{-2}, and 178 patients (33.8%) were diagnosed as having CKD. Table 1 shows the clinical background and values of laboratory parameters in the CKD and non-CKD groups. The patients in the CKD group were significantly older than those in the non-CKD group, the rates of hypertension and diabetes mellitus were higher, and they showed a slight decrease of hemoglobin. The concentrations of serum Cys C and plasma BNP were higher in the CKD group, but there was no difference in LVEF between

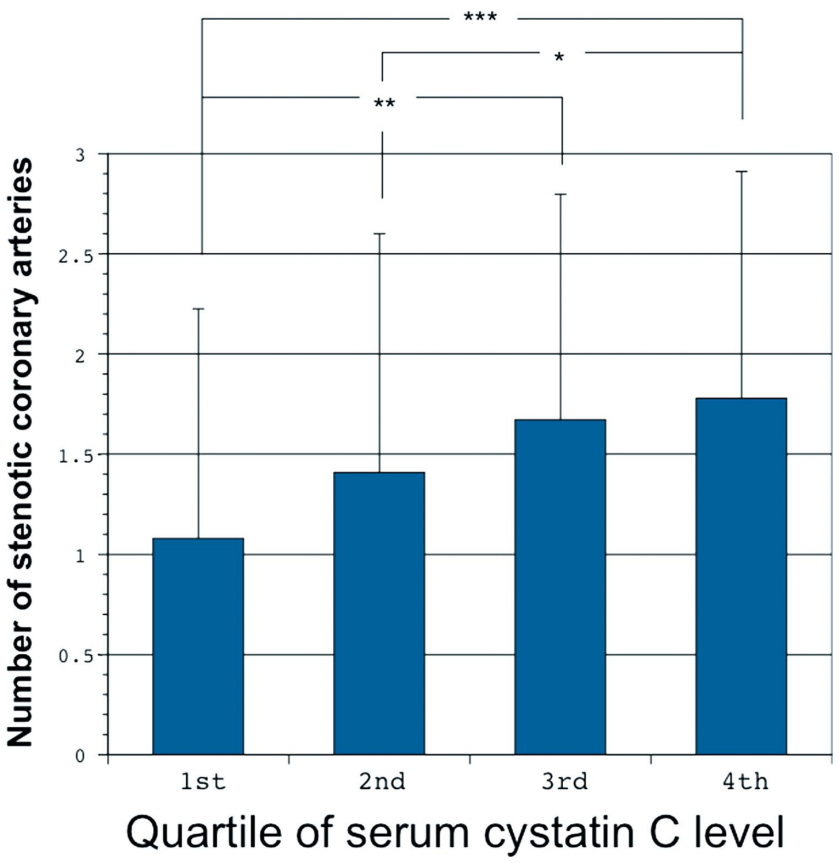

Figure 4. Distribution of patients by the concentration of serum cystatin C and number of stenotic coronary arteries *P<0.05, **P<0.001, ***P<0.0001.

Table 2. Clinical Background of Non-CKD Patients Distributed Into Those With a Normal Concentration of Cys C and Those With an Elevated Concentration of Cys C

	Normal Cys C	High Cys C	P value
N	205	143	
Age (years old)	63.3±9.5	68.6±8.7	<0.0001
Sex (M/F)	141/64	122/21	<0.0001
Hypertension (%)	82.9	88.8	0.127
Dyslipidemia (%)	76.1	69.9	0.199
Diabetes mellitus (%)	33.2	43.4	0.053
Smoking habit (%)	42.9	42.0	0.857
Prior MI (%)	10.7	13.3	0.467
HbA_{1c} (%)	6.00±1.16	5.91±1.06	0.471
Hb (g/dl)	13.8±1.4	13.7±1.5	0.580
SCr (mg/dl)	0.72±0.13	0.82±0.12	<0.0001
Cys C (mg/L)	0.79±0.07	1.03±0.11	<0.0001
GFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	79.9±13.7	70.3±9.3	<0.0001
BNP (pg/ml)	34.1±48.2	57.4±70.3	0.0003
LVEF (%)	57.7±11.9	58.0±11.6	0.862
Number of stenotic arteries			
0	82	31	0.0046
1	47	41	
2	31	30	
3	45	41	

Data are expressed as the mean±SD or percentage.
Abbreviations see in Table 1.

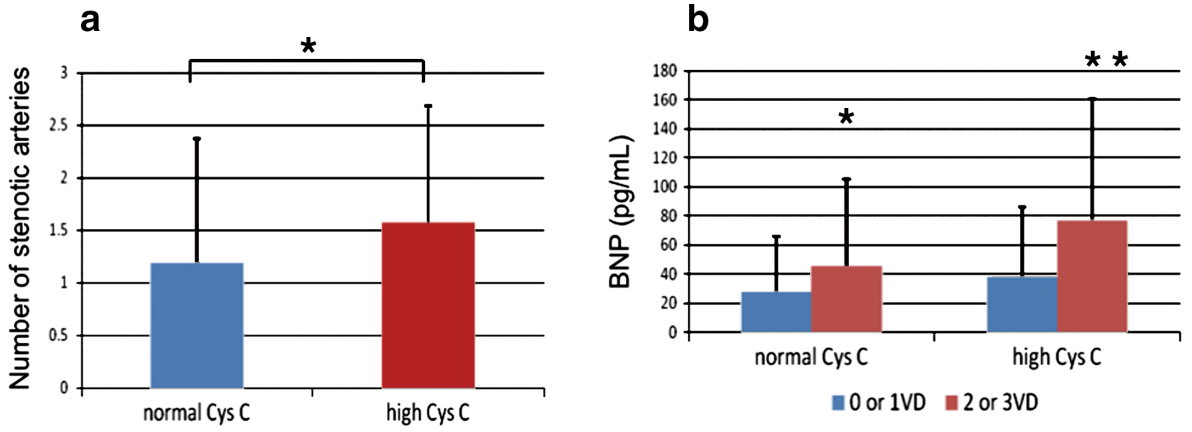

Figure 5. Mean number of stenotic coronary arteries (**a**; *P<0.01 vs normal Cys C) and plasma BNP level (**b**; *P<0.01, **P< 0.001 vs 0 or 1 VD) in non-CKD patients with a normal and high concentration of Cys C. Cys C, cystatin C; BNP, B-type natriuretic peptide; VD, vessel disease; CKD, chronic kidney disease.

Table 3. Association of Cardiovascular Risk Factors With Risk of Having Multiple-Vessel Disease

	No. patients	Frequency of multiple-vessel disease (%)	OR (95%CI)	P value
Hypertension				<0.001
No	49	16.3	1.00 (reference)	
Yes	299	46.5	3.98 (1.79–8.87)	
Dyslipidemia				0.055
No	91	34.1	1.00 (reference)	
Yes	257	45.1	1.67 (0.99–2.80)	
Diabetes mellitus				0.567
No	218	40.4	1.00 (reference)	
Yes	130	45.4	1.14 (0.73–1.80)	
Cys C				0.043
Normal	205	37.1	1.00 (reference)	
High	143	49.7	1.60 (1.02–2.51)	

OR, odds ratio; CI, confidence interval. Other abbreviation see in Table 1.
ORs were adjusted for age and sex.

the 2 groups. Figure 2 shows the distribution of patients in the CKD group and non-CKD group by the number of stenotic coronary arteries. As shown in Figure 2, the number of stenotic coronary arteries was significantly higher in the CKD group (non-CKD vs CKD; 1.34±1.17 vs 1.76±1.14 VD; P<0.001).

In all cases, there was a close and positive correlation between the concentration of SCr and that of plasma Cys C (R^2=0.667, P<0.001). Such a close and positive correlation was also seen in the CKD group (R^2=0.649, P<0.001), whereas no significant correlation was observed in the non-CKD group (R^2=0.186, NS; Figure 3). There was a significant negative correlation between the serum concentration of Cys C and GFR in all cases (R^2=0.378, P<0.001), while there was no significant correlation between these 2 parameters in the non-CKD group. All the cases were divided into quartile groups based on the serum concentration of Cys C to examine its correlation with the number of stenotic coronary arteries in each group. As shown in Figure 4, the number of stenotic coronary arteries was larger in the quartiles with higher concentrations of serum Cys C.

Of the 348 non-CKD patients, 143 (41.1%) had a Cys C concentration higher than the normal reference value (Cys C concentration >0.90 mg/L). Thus, non-CKD patients were further divided into 2 groups by the upper limit of the reference value (0.90 mg/L): normal Cys C concentration group: 205 (58.9%) cases; and high Cys C concentration group: 143 (41.1%) cases. Table 2 shows the clinical background and values of laboratory parameters for these 2 groups. The patients in the high Cys C concentration group were significantly older than those in the normal Cys C concentration group and the number of men was significantly higher. However, there was no difference in the rate of patients with hypertension, dyslipidemia or diabetes mellitus. A significant difference in GFR (approximately 10 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) was seen between these groups. The plasma BNP level was higher in the high Cys C concentration group, whereas there was no significant difference in LVEF. As for the severity of coronary artery stenosis in these groups, the number of stenotic coronary arteries was significantly higher in the high Cys C concentration group (Figure 5). A similar analysis was performed in terms of GFR, and the result showed that there was

no significant difference in the number of stenotic arteries between the normal and high Cyc C groups in patients with a GFR of ≥90 ml·min^{-1}·1.73 m^{-2} or in those with a GFR of 75–90 ml·min^{-1}·1.73 m^{-2}. In patients with a GFR of 60–75 ml·min^{-1}·1.73 m^{-2} and a high concentration of Cys C, however, the number of stenotic coronary arteries was significantly larger [1.65±1.11 (n=104) vs 1.08±1.14 (n=88), P<0.001]. Multiple logistic regression analysis revealed that besides hypertension, high Cys C was a significant risk factor for multiple-VD (2 or 3 VD) after being adjusted for age and sex (**Table 3**).

The BNP level was high in the group with multi-vessel CAD. It was 35±66 pg/ml in the 0 or 1-vessel CAD group (n=201) and 66±90 pg/ml (P=0.0003) in the 2 or 3-vessel CAD group (n=147). The difference was even more significant among non-CKD patients with a high concentration of Cys C.

Discussion

In the present study, we confirmed that CAD in patients with CKD was significantly more severe than in those without CKD. This might explain the reported higher frequency of cardiovascular events associated with a decline in renal function.[1–4] Yet, the increase of cardiovascular events was demonstrated in CKD patients whose renal disease was classified according to GFR, which was calculated solely using the concentration of SCr. This parameter is known to be affected by many factors other than GFR, such as age, sex, muscle mass, and physical activity level. In elderly patients and patients with a mild decline of renal function, therefore, the GFR assessed based on the level of SCr might be biased. In fact, some studies have reported that the blood level of Cys C predicted the occurrence of cardiovascular complications or the resultant death more accurately than SCr, GFR or creatinine clearance.[16,17] Shlipak et al found that in non-CKD subjects with a high serum concentration of Cys C, cardiovascular events and death occurred at a higher incidence as compared with the group with a low plasma concentration of Cys C.[18]

The present study showed that the level of serum Cys C correlated with the severity of CAD in all the subjects of this study including CKD patients. This was consistent with the findings of previous studies.[19,20] Serum Cr level or GFR estimated by serum Cr is a well-known indicator of prognosis after acute myocardial infarction,[4] and Cys C was reported to have the same predictive value.[21,22] In this study, 40.8% of the patients without CKD, as assessed based on the concentration of SCr, showed an increase of plasma Cys C, and CAD was significantly more severe than in non-CKD patients with a normal concentration of serum Cys C. There was no significant correlation between SCr and the concentration of serum Cys C in the non-CKD group. The results of this study indicated that patient classification based on GFR estimated from the concentration of SCr might overlook those with very early stage renal dysfunction as well as those at risk of worsening CAD. Therefore, Cys C is a more sensitive marker of slight decline in renal function than SCr. Moreover, increases in serum Cys C appear to indicate severity of CAD, suggesting its clinical usefulness.

It remains unclear whether this is simply because the concentration of plasma Cys C exactly reflects renal function or reflects other predictors of the patient prognosis. The relationship of serum Cys C with the inflammatory response (increased CRP and proinflammatory cytokines) frequently associated with the decline in renal function is under study, but no clear conclusion has been reached yet.[23]

In contrast, some studies have shown that the concentration of serum Cys C is influenced, although less frequently, by various factors such as thyroid dysfunction,[24] steroid therapy,[25] some types of cancer,[26] Alzheimer's disease,[27] and HIV infection.[28] These factors were not present in the subjects of this study. Another study reported that the concentration of serum Cys C was also influenced by age, sex, muscle mass, etc. but not to the extent SCr is influenced by these factors.[29]

The possibility that Cys C might directly influence the occurrence of cardiovascular disease has been raised. In fact, some studies have demonstrated that the content of Cys C decreases in the tissues of animals and people with atheromatous plaques and aneurysms.[30,31] Aneurysms often occur in Cys C gene knockout mice.[32] If this were true for humans, coronary disease would occur in those with a low concentration of Cys C, and would contradict the results of our study. Niccoli et al found that the concentration of blood Cys C was directly proportional to the number of stenotic lesions in 70 patients with acute coronary syndrome. Based on the fact that their GFR was normal (≥90 ml·min^{-1}·1.73 m^{-2}), Cys C was thought to play some role in plaque formation.[33] Our study, however, demonstrated no clear relationship between Cys C and the number of stenotic coronary arteries in patients with normal renal function, and provided no evidence of a direct relationship between Cys C and arteriosclerosis.

BNP is widely used as a marker of cardiac diseases in clinical practice, and not only as a marker of heart failure, that is, not only reflecting abnormal intracardiac hemodynamics, BNP is also greatly affected in patients with cardiac hypertrophy, arrhythmia, deficient renal clearance, etc.[34] BNP was increased in our patients with CKD although LVEF did not decrease, and this might be attributable to left ventricular diastolic dysfunction[35] or the factors mentioned above. Among the patients without CKD, BNP was significantly higher, although LVEF did not decrease in the multi-vessel CAD group, especially in those with a high concentration of plasma Cys C. CAD is well known to gradually worsen in patients with CKD. We found that CAD had probably worsened in some patients with a GFR of approximately 70 ml·min^{-1}·1.73 m^{-2}, although they did not have CKD (ie, patients whose GFR estimated from SCr was ≥60 ml·min^{-1}·1.73 m^{-2}). Measurements of both Cys C and BNP are believed to be useful to detect the occurrence of CAD.

Study Limitations

The precise method to evaluate the severity of CAD has been debated until now. In the present study, we used only the number of stenotic coronary arteries. This is the classical method of evaluation, although the number of diseased vessels itself was reported to indicate the patient's prognosis with a high degree of certainty.[36] Since Gensini reported in 1983 a scoring system using the morphology of diseased coronary arteries to try to evaluate the severity more accurately,[37] a lot of systems based on morphological findings have been proposed, including the newest one, SYNTAX scoring. One possible disadvantage in this study is that we did not apply any of these scoring systems. Moreover, although now we are able to examine coronary arteries in more detail using new imaging techniques such as intravascular ultrasonography, and thereby evaluate the patients' prognosis more accurately, many of our patients underwent CAG only and those techniques were not an option in terms of health insurance coverage.

The information related to cardiovascular events in this group of patients is not available because we assessed a relatively new group of patients and thus we could follow them for only a few years. We might add new information about their clinical course after we gather data related to cardiovascular events.

Conclusion

Cys C proved to be a more sensitive marker of mild decline in renal function than SCr. In patients with CAD, an increase in the plasma concentration of Cys C indicates severity of coronary lesions. As the presence of CAD is one of the major determinants of the prognosis in patients with reduced renal function, the concentration of serum Cys C is expected to be useful in detecting patients at risk of CAD.

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