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Increased pre-procedural urinary microalbumin is associated with a risk for renal functional deterioration after coronary computed tomography angiography

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ABSTRACT

Background: Urinary microalbumin is a marker for preclinical nephropathy. A percentage change in cystatin C (%CyC) of ≥10% for 24 h after tests with contrast media is reportedly an independent predictor for developing contrast-induced nephropathy. We investigated the relationship between the presence of urinary microalbumin and changes in CyC after coronary computed tomography angiography (CCTA).
Methods: Three hundred and thirty-three patients with known or suspected coronary artery disease who scheduled for CCTA using a 70 mL of Iopamidol were enrolled. Serum creatinine and CyC levels were measured at baseline and 24 h post-procedure. The %CyC, absolute changes in estimated glomerular filtration rate (ΔeGFR), and oral fluid volume from pre- to post-procedure were calculated. The patients were dichotomized into 2 groups as follows: group A comprised 83 patients showing a %CyC of ≥10%; and group B comprised 250 patients showing a %CyC of <10%.
Results: The ΔeGFR, fasting plasma glucose levels, HbA1c, and pre-procedural urinary microalbumin levels were significantly greater in group A than in group B. Oral fluid intake volume was significantly less in group A than in group B. The urinary microalbumin significantly correlated with %CyC ($r = 0.504$, $P < 0.0001$). Multivariate logistic regression analysis revealed that pre-procedural urinary microalbumin and oral fluid volume were independent predictors for %CyC ≥ 10%. The optimal cut-off value of a pre-procedural urinary microalbumin level was 58 mg/g·creatinine for predicting a %CyC ≥ 10% using receiver-operating-characteristic analysis.
Conclusions: Renal functional changes should be carefully paid attention to after CCTA, particularly in patients exhibiting increased pre-procedural urinary microablumin levels.
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1. Introduction

Coronary computed tomography angiography (CCTA) has emerged as a common and convenient test for evaluating coronary atherosclerosis. This modality is often used to exclude patients who have clinically significant coronary artery disease from those who exhibit atypical chest symptoms with a low likelihood of significant coronary artery disease because of an extremely high negative predictive value [1,2]. However, a relatively high dose of contrast media is required for this imaging technique. Accordingly, its use is prohibited for patients with overt renal dysfunction, and care should be taken for renal functional deterioration after the procedure even in patients with preserved renal function.

Serum cystatin C (CyC) is considered to be a more sensitive marker for evaluating renal function than either serum creatinine or creatinine-based estimated glomerular filtration rate (eGFR) [3–5]. A recent study demonstrated that a percentage change in CyC (%CyC) of ≥10% for 24 h after tests with contrast media is an independent predictor for developing contrast-induced nephropathy in patients undergoing emergency coronary intervention [6]. Thus, serum CyC plays a role as a key biomarker in the early detection of contrast-induced acute kidney injury.

The presence of urinary microalbumin indicates an increased risk for developing nephropathy and subsequent renal failure, particularly in diabetic patients [7–9]. The presence of microalbuminuria may reflect a generalized defect in vascular permeability and concomitant atherogenetic diathesis [10]. Urinary microalbumin levels of 30–299 mg/g·creatinine are considered to be the status of significant proteinurea and an indicator of preclinical renal dysfunction [11].

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Generally, the degree of acute kidney injury is very likely to be related to the degree of pre-existing functional impairment [12]. However, a previous study indicated that 4.3% of the patients with normal renal function experienced CIN after cardiac catheterization and the presence of proteinuria was associated with CIN after the procedure [13]. In our previous studies, some patients experienced renal functional deterioration after CCTA even though they had normal renal function and a relatively smaller amount of contrast medium (70 mL) was administered, as compared to catheter-based interventional procedure [14,15], and another study indicated importance of oral fluid intake after CCTA for prophylaxis [16]. In addition, elevated urinary microalbumin and low hydration were independent predictors for renal functional deterioration after CCTA in only diabetic patients [17]. Therefore, investigating the effects of the presence of microalbuminuea on renal function after the use of contrast media is really of interest.

In the present study, we evaluated changes in renal function using CyC, investigated factors associated with renal functional deterioration, and examined the relationship between pre-procedural urinary microalbumin levels and a 10% increase in CyC 24 h after CCTA in various patients with preserved renal function.

2. Methods

Consecutive 333 patients with suspected or known coronary artery disease scheduled for CCTA were retrospectively analyzed on admission to our hospital. Patients were excluded prior to the study if they had any of the following: overt kidney disease (eGFR <60 mL/min/1.73 m^2 and/or urinary microalbumin level > 300 mg/g·creatinine); atrial fibrillation; unstable clinical conditions; uncontrolled bronchial asthma; thyroid diseases; an inability to follow breath-hold command; and pregnancy. Patients who were allergic to iodine-containing contrast medium were also excluded. Biganide agents which induce lactate acidosis were discontinued for 48 h before administration of a contrast medium.

The study protocol was approved by the Ethical Committee of Kami-iida Dai-ichi General Hospital, and given informed consent was obtained from each patient.

All patients admitted to our hospital, and they were with fasting condition at least for 6 h before CCTA. An intravenous saline (0.9%, 500 mL) was given for hydration before administration of a contrast medium. All patients received sublingual nitroglycerin (0.3 mg). An intravenous beta-blocker, landiolol hydrochloride (0.0039 ± 0.0012 mg/kg/min; Onoact, Ono Pharmaceutical Co, Osaka, Japan) was given if heart rates were over 70 bpm. Seventy mL of a non-ionic contrast medium with low-osmotic, high-iodine content, Iopamidol (Oypalomin 370, Konica-Minolta, Japan) was intravenously administered at a rate of 5 mL/min, and subsequently, retrospectively ECG-gated CCTA was conducted with a 64-row multi detector CT (Definition Edge, Siemens Medical Solutions, Forchheim, Germany) with a gantry rotation time of 0.28 s/rotation, breath-hold time of 6.5 s, collimation of 128 × 0.6 mm, table feed of 3.8 mm/rotation, pitch factor of 0.17 (automatically adapted to the patients' heart rate), quality reference of 200 mA, tube voltage of 100 to120 kVp, and ECG pulse window of 20–70% of the ECG R-R interval. The spiral acquisition was performed.

Blood samples were taken from the antecubital veins. Serum creatinine and CyC levels were measured before and 24 h after CCTA. The eGFR was calculated according to the previously recommended formula [18]. The absolute changes in eGFR (ΔeGFR), the absolute changes in CyC (ΔCyC), and %CyC were calculated as follows:

$$\Delta eGFR = 24\text{ h post-procedural eGFR} - \text{pre-procedural eGFR}$$
$$\Delta CyC = 24\text{ h post-procedural CyC} - \text{pre-procedural CyC}$$
$$\%CyC = \Delta CyC / \text{pre-procedural CyC} \times 100.$$

Urinary microalbumin was measured by immunonephelometry [19]. Data were corrected for urinary creatinine and expressed as a microalbumin-creatinine ratio.

All patients were recommended to intake as much oral fluid as possible. The unrestricted oral fluid volume was measured by nurses during hospital admission.

Using echocardiography, left ventricular end-diastolic and systolic diameters were measured and left ventricular ejection fraction was calculated according to the standard methods [20].

All patients were dichotomized into 2 groups based on a 10% increase in %CyC 24 h after CCTA as follows: group A comprised 83 patients showing a %CyC of ≥10%; and group B comprised 250 patients showing a %CyC of <10%.

Data were presented as mean ± SD and categorical variables as a number (percentage). An unpaired *t*-test was used between the 2 groups and a chi-square test was used for the comparison of 2 proportional differences. A linear regression analysis was performed for the relations between continuous variables. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for each variable were calculated by a univariate logistic regression analysis. A multivariate logistic regression analysis was applied to determine the independent predictors for a %CyC ≥ 10%. Variables showing $P < 0.10$ on the univariate analysis were entered into the multivariate analysis. Furthermore, a receiver-operating characteristic analysis was performed to determine the optimal cutoff value of a urinary microalbumin level for predicting a %CyC ≥ 10%. A $P < 0.05$ was considered statistically significant.

3. Results

A total of 333 patients (155 men with a mean age of 67 ± 10 years) were enrolled in this study. Patient characteristics are listed in Table 1. Cardiovascular risk factors were distributed as follows: 245 (74%) patients with hypertension; 150 (45%) with dyslipidemia; 136 (41%) with diabetes mellitus; and 161 (48%) with a smoking habit. The mean HbA1c was 6.1 ± 3.9%. The pre-procedural eGFR, post-procedural eGFR, and ΔeGFR levels were 70.8 ± 11.1 mL/min/1.73 m^2, 69.2 ± 14.4 mL/min/1.73 m^2, and −1.6 ± 6.1 mL/min/1.73 m^2, respectively. The mean pre-procedural CyC, post-procedural CyC, ΔCyC, and %CyC were 0.71 ± 0.11 g/L, 0.75 ± 0.15 g/L, 0.04 ± 0.04 g/L, and 5.6 ± 8.7%, respectively. The mean pre-procedural urinary microalbumin level was 39.1 ± 142.8 mg/g·creatinine. The mean left ventricular ejection fraction was 69.0 ± 9.9%, and the mean oral fluid intake volume was 1229 ± 742 mL.

Comparisons of variables between the 2 groups are also listed in Table 1. The percentage of diabetic patients, fasting glucose levels, HbA1c, and pre-procedural microalbumin levels were significantly greater in group A than in group B (55% vs 45%, $P = 0.003$; 114 ± 34 mg/dL vs 101 ± 26 mg/dL, $P = 0.001$; 6.5 ± 1.4% vs 5.9 ± 1.0%, $P < 0.0001$; 78.3 ± 60.0 mg/g·creatinine vs 25.5 ± 30.4 mg/g·creatinine, $P < 0.0001$, respectively). In renal function, the post-procedural eGFR was significantly less in group A than in group B (66.1 ± 14.2 mL/min/1.73 m^2 vs 70.9 ± 17.7 mL/min/1.73 m^2, $P = 0.002$), and the ΔeGFR, post-procedural CyC, and ΔCyC were significantly greater in group A than in group B (−4.5 ± 6.8 mL/min/1.73m^2 vs −0.6 ± 6.7 mL/min/1.73m^2, $P = 0.001$, 0.83 ± 0.19 g/L vs 0.72 ± 0.17 g/L, $P < 0.0001$, and 0.10 ± 0.06 g/L vs 0.01 ± 0.04 g/L, $P < 0.0001$, respectively). Oral fluid intake volume was significantly less in group B than in group A (853 ± 407 mL vs 1353 ± 585 mL, $P < 0.0001$).

A significant correlation was observed between pre-procedural urinary microalbumin and %CyC ($r = 0.504$, $P < 0.0001$) (Fig. 1) as well as between pre-procedural urinary microalbumin and ΔCyC ($r = 0.439$, $P < 0.0001$). A significant correlation was also observed between HbA1c and %CyC, but the correlation was very weak ($r = 0.220$, $P = 0.03$) (Fig. 2).

In the univariate logistic regression analysis, smoking habit, high-density lipoprotein cholesterol, fasting glucose levels, HbA1c, urinary microalbumin levels, and oral fluid intake volume were associated with a %CyC ≥ 10%, while the multivariate logistic regression analysis revealed that pre-procedural urinary microalbumin levels and oral fluid intake volume were independent predictors for a %CyC ≥ 10% (OR: 1.998, 95% CI: 1.027–2.901, $P < 0.0001$; and OR: 0.878, 95% CI: 0.624–0.995, $P < 0.0001$, respectively) (Table 2).

Using the receiver-operating-characteristic curve analysis, the optimal cut-off value of a pre-procedural urinary microalbumin level was 58 mg/g·creatinine for predicting a %CyC ≥ 10% with sensitivity, specificity, and area under the curve of 74%, 81%, and 0.84, respectively (Fig. 3).

4. Discussion

In CCTA, the use of a relatively high dose of iodine-content contrast media may induce the development of contrast-induced renal functional deterioration, even in patients without overt renal dysfunction. Accordingly, it is important to use reliable methods to detect patients prone to show post-procedural renal functional deterioration, and a proper prophylaxis should be established. However, up to now, an effective prophylaxis except for hydration has not been reported [21,22].

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