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Original article

Relationship between pre-procedural microalbuminuria and renal functional changes after coronary computed tomography in diabetic patients

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ABSTRACT

Background: Diabetes is one of the risks for development of contrast-induced nephropathy (CIN). The percentage change in cystatin C (CyC), a recent new reliable marker for detecting subtle renal dysfunction, of ≥10% for 24 h after procedure is an independent predictor for developing CIN. Urinary microalbumin is one of the markers for preclinical nephropathy in diabetic patients. We investigated the relationship between pre-procedural urinary microalbumin and renal functional changes using CyC after coronary computed tomography angiography (CCTA) in diabetic patients.

Methods: Two hundred and six patients with diabetes scheduled for CCTA were enrolled. The serum creatinine and CyC levels were measured before and 24 h after CCTA. The percentage change in CyC (%CyC) and absolute change in estimated glomerular filtration rate (eGFR) from pre- to post-procedure were calculated. The pre-procedural urinary microalbumin was measured. The patients were classified into 2 groups as follows: group A comprised 93 patients with pre-procedural urinary microalbumin of ≥30 mg/g creatinine; and group B comprised 113 patients with one of <30 mg/g creatinine.

Results: The %CyC, fasting plasma glucose levels, and HbA1c were significantly greater in group A than in group B. The absolute change in eGFR was significantly less in group A than in group B. A significant correlation was seen between urinary microalbumin and %CyC ($r = 0.49$, $p < 0.0001$). Multivariate regression analysis revealed that pre-procedural urinary microalbumin and HbA1c were independent predictors for a %CyC ≥ 10% (OR: 1.030, 95% CI: 1.020–1.039, $p = 0.008$; and OR: 1.011, 95% CI: 1.007–1.016, $p = 0.004$, respectively). The optimal cut-off value of a pre-procedural urinary microalbumin level was 64 mg/g creatinine for predicting a %CyC ≥ 10% using receiver-operating characteristic curve analysis with a sensitivity, specificity, and area under the curve of 56%, 88%, and 0.72, respectively.

Conclusions: Renal functional changes should be paid attention to after CCTA, particularly in diabetic patients exhibiting elevated pre-procedural urinary microalbumin even though they indicate preserved eGFR.

Introduction

Cardiovascular imaging modalities with the use of contrast medium have been expanded worldwide in the clinical setting. Of those, coronary computed tomography angiography (CCTA) is a contemporary, convenient examination and has been commonly applied for detecting significant coronary atherosclerosis in patients with a low likelihood but suspected coronary artery disease because of an extremely high negative predictive value [1,2]. However, any repetitive use of CCTA must be approached with special caution because this examination calls for the use of a relatively high dose of iodine-containing contrast media. This examination is contraindicated for subjects with overt kidney dysfunction. In addition, some patients are required to undergo

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subsequent diagnostic coronary angiography and/or therapeutic coronary angioplasty, eventually being concerned about additional exposure to contrast medium. Thus, the early detection of patients who are prone to show post-procedural renal functional deterioration prior to this examination using reliable renal markers is crucial.

Cystatin (CyC) is a basic protein that comprises 120 amino acids with a molecular weight of 13 kDa [3]. CyC is freely filtered by the glomerulus and completely re-absorbed and catabolized by the proximal tubules without re-absorption into the bloodstream [4,5]. Since the serum CyC levels are not affected by age, sex, and lean muscle mass, it is a new sensitive marker for detecting the presence of potential renal dysfunction. Previous studies have reported that this is a more reliable endogeneous marker of glomerular filtration rate (GFR) than serum creatinine [6,7]. It has been demonstrated that the percentage change in CyC (%CyC) of $\geq$10% for 24 h after tests with contrast media is an independent predictor for developing contrast-induced nephropathy (CIN) in patients undergoing emergency coronary intervention [8]. Thus, serum CyC is a key biomarker in the early detection of contrast-induced acute kidney injury.

Diabetes mellitus has reached epidemic populations and has become a major health problem. The number of diabetic patients is expected to increase exponentially and the onset is occurring at even younger ages. Because atherosclerotic cardiovascular diseases often coexist in diabetic patients, coronary evaluations with the use of contrast media are mandatory in diabetic patients with suspected coronary artery disease. Diabetes is also one of the risks for development of CIN [9,10]. In addition, diabetic patients often have the presence of urinary microalbumin, which is a potential marker of subclinical renal dysfunction and associated with future diabetic nephropathy [11]. Therefore, attention should be paid to the use of contrast medium in diabetic patients exhibiting microalbuminuria. In our previous study including nondiabetic patients, we demonstrated that the percentage of patients showing a %CyC of $\geq$10% after CCTA is significantly greater in diabetic patients than in nondiabetic patients, and that pre-procedural microalbuminuria is a predictor for a %CyC of $\geq$10% in that population [12]. Therefore, it is of interest to investigate the effects of the pre-procedural microalbumin on renal functional changes after CCTA in only diabetic patients.

In this study, we investigated the relationship between pre-procedural urinary microalbumin and 10% increase in CyC for 24 h after CCTA in diabetic patients.

Methods

Study population

In this study, 206 consecutive patients with suspected or known coronary artery disease scheduled for CCTA between October 2011 and May 2012 were enrolled. Patients were excluded prior to the study if they had any of following: overt kidney disease [estimated GFR (eGFR) $<$ 60 mL/min/1.73 m^2 or urinary microalbumin level $\geq$ 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. Biguanide agents against diabetes, which have a possibility to induce acute lactic acidosis, were discontinued for 48 h before administration of contrast medium.

Renal function before and 24 h after CCTA and pre-procedural urinary microalbumin were measured, and the relationship between pre-procedural microalbumin and renal functional changes after CCTA was examined. Variables that predict renal functional deterioration after adjusting confounders such as age, gender, hypertension, dyslipidemia, diabetic status, smoking status, cardiac function, and pre-procedural renal function were analyzed.

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

CCTA

All patients were in a fasting condition before CCTA, and an intravenous saline (0.9%, 500 mL) was given for hydration before administration of contrast medium. Sublingual nitroglycerin (0.3 mg) was given, and an intravenous beta-blocker, landiolol hydrochloride (0.0039 $\pm$ 0.0012 mg/kg/min; Onoact, Ono Pharmaceutical Co., Osaka, Japan), was given if heart rates were over 70 bpm [13]. Non-ionic contrast medium (70 mL) with low-osmotic, high-iodine content iopamidol (Oypalomin 370, Konica-Minolta, Tokyo, Japan) was intravenously administered at a rate of 5 mL/min, and subsequently CCTA was conducted on 64-row multi-detector CT (Definition Edge, Siemens Medical Solutions, Forchheim, Germany). The contrast-enhanced imaging using electrocardiographic gating was obtained during a single held breath with a gantry rotation time of 0.28 s/rotation, breath-hold time of 6.5 s, collimation of 128 mm $\times$ 0.6 mm, table feed of 3.8 mm/rotation, pitch factor of 0.17, quality reference of 200 mA, and tube voltage of 100–120 kVp.

Renal function and measurement of urinary microalbumin

Blood samples were obtained from the antecubital veins. The serum creatinine and CyC levels were measured before and 24 h after CCTA. The eGFR was calculated according to the recommendation criteria [14], and the absolute changes in eGFR (ΔeGFR) and %CyC were calculated as the following equations:

$$\Delta\text{eGFR} = \text{24-hour post-procedure eGFR} - \text{pre-procedure eGFR}$$
$$\%\text{CyC} = (\text{24-hour post-procedure CyC} - \text{pre-procedure CyC})/\text{pre-procedure CyC} \times 100$$

Urinary microalbumin was measured by immunonephelometry [15]. Data were corrected for urinary creatinine and expressed as a microalbumin–creatinine ratio.

Measurement of cardiac function

Echocardiography was conducted to calculate left ventricular function. The left ventricular ejection fraction was calculated after measuring end-diastolic and systolic diameters on the 2-dimensional echocardiographic mode according to the standard methods [16].

Patient classification

All patients were classified into 2 groups according to the pre-procedural urinary microalbumin levels as follows: group A comprised 93 patients with a pre-procedural urinary microalbumin of $\geq$30 mg/g creatinine; and group B comprised 113 with one of $<$30 mg/g creatinine.

Statistical analysis

Data were presented as mean $\pm$ SD and categorical variables as a number (percentage). An unpaired *t*-test was used between the 2 groups and a Chi-square analysis was used for comparison of 2 proportional differences. A Mann–Whitney *U*-test and Fisher's exact test were applied if appropriate. A linear regression analysis was performed for the relations between continuous variables. A

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