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Serum cystatin C is associated with early stage coronary atherosclerotic plaque morphology on multidetector computed tomography

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ABSTRACT

Objective: Cystatin C, a novel marker of kidney function, has been reported to be a predictor of adverse cardiovascular outcomes in patients without established chronic kidney disease. However, the relationship between serum cystatin C concentrations and early stage coronary atherosclerotic plaque morphology among patients with preserved kidney function has not been fully evaluated.
Methods and results: 405 outpatients with early coronary artery disease with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2 and <50% stenosis on 64-slice CT coronary angiography were enrolled. Subjects were categorized into quartiles by serum cystatin C (quartile I: ≤0.88 mg/L – quartile IV: ≥1.16 mg/L). Plaques in coronary segments were categorized as calcified or noncalcified. Multiple linear regression analysis revealed that lower eGFR, higher age, increasing numbers of noncalcified and calcified plaques, lower high-density lipoprotein cholesterol, and female gender were statistically significant predictors of increased cystatin C concentrations. The risk for presence of noncalcified plaques increased significantly with increasing quartiles of cystatin C. Compared with those in the lowest quartile, patients in each subsequent quartile were at steadily increased risk of having noncalcified plaque (quartile IV: OR 5.6; 95% CI 2.3–13.9, p-value <0.001). Both number of segments with calcified plaque and Agatston score were highly correlated with cystatin C concentrations (both $p < 0.001$), but when adjusted for segments with noncalcified plaque and other risk factors, calcified plaque segments were no longer independently predictive.
Conclusion: Higher serum cystatin C concentrations were correlated with early stage coronary atherosclerotic plaques among patients without established chronic kidney dysfunction. Noncalcified plaques increased with serum cystatin C concentrations, an association independent of eGFR and other cardiovascular risk factors.

1. Introduction

Cystatin C, a member of the cysteine superfamily of endogenous cysteine protease inhibitors synthesized in all nucleated cells [1,2] has been proposed as a more reliable marker of renal function than serum creatinine [3]. Previous literature suggests that a graded association exists between higher serum cystatin C and increased CVD prevalence in patients without established chronic kidney disease [4]. Cystatin C is also reported to be a prognostic biomarker of risk for adverse cardiovascular outcomes among elderly persons with estimated GFR ≥ 60 ml/min/1.73 m^2 [5]. However, the relationship between cystatin C and early stage coronary atherosclerotic plaque morphology among patients without established kidney dysfunction has not been fully evaluated. Considering that patients with early stage coronary artery disease (CAD), defined as nonobstructive stenosis (<50% luminal narrowing), are at elevated risk compared to patients without CAD [6], optimal methods to assess early stage coronary plaque are necessary for preventing adverse cardiac events.

Abbreviations: MDRD, modification of diet in renal disease; MDCT, multidetector computed tomography; eGFR, estimated glomerular filtration rate; CTCA, computed tomography coronary angiography; CAD, coronary artery disease; CAC, coronary artery calcification.

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At present, multidetector-row computed tomography (MDCT) is a useful tool for detection of early stage coronary atherosclerosis with nonobstructive stenosis [7]. In addition, both calcified and noncalcified lesions are visualized on MDCT [8]. Information on plaque morphology from MDCT has been reported to provide additional incremental prognostic value compared to a baseline clinical risk model, with the presence of noncalcified plaques found to be the strongest predictor for cardiac events [9].

In our study, we evaluated the association between serum cystatin C concentrations and early stage coronary atherosclerotic plaque among patients without established kidney dysfunction. In addition, we investigated whether differences in atherosclerotic plaque morphology on MDCT are associated with increasing cystatin C concentrations.

2. Methods

2.1. Participants

This was a cross-sectional study designed to investigate the correlation between serum cystatin C concentrations and early stage coronary atherosclerotic plaques and their morphology. Between July 2007 and September 2010, a total of 405 patients who met inclusion requirements in the Cardiovascular Center at Amagasaki Central Hospital in Amagasaki, Japan, were enrolled in this study. CTCA was performed on patients with typical or atypical chest pain, a positive or equivocal exercise test, high cardiovascular risk profile, and no contraindication to iodinated contrast agents, following the recommended 2006 criteria for cardiac CT [10]. Patients were included in this study if they met all of the following criteria: (1) estimated GFR (eGFR) $\geq$60 ml/min using MDRD formula, (2) CT angiographic evidence of <50% stenosis in any vessel, and (3) cystatin C measurements drawn within one month prior to CTCA. Patients were excluded if they had a history of coronary heart disease defined as prior percutaneous coronary intervention, coronary artery bypass grafting, or ejection fraction assessed by ultrasound <60%. All aspects of the study were approved by the institutional review board, and all study participants provided written informed consent.

A diagnosis of hypertension was identified if patients had any of the following: self-reported the diagnosis on questionnaire, were taking antihypertensive medications, had an average systolic blood pressure $\geq$140 mmHg on 2 separate measurements or an average diastolic pressure of $\geq$90 mmHg. Patients were regarded as having diabetes if they met 2010 American Diabetes Association criteria [11] or were taking anti-hyperglycemic medications.

2.2. Laboratory assay

After patients had fasted overnight, a single sample of blood was drawn for analysis. Serum cystatin C concentrations were measured from venous samples using BioMajesty JCA-BM 8060 (JEOL Corporation, Tokyo, Japan) and Auto Cystatin C-BML (BML Corporation, Saitama, Japan) assay with latex agglutination method. Inter-assay and intra-assay coefficient of variance were reported to be 1.7% and 1.8%, respectively. Serum creatinine was measured by Accurues Auto CRE (Cynotest Corporation, Kanagawa, Japan). Estimated GFR was calculated by MDRD formula as follows: eGFR (ml/min/1.73 m^2) = 175 $\times$ serum creatinine (mg/dl)$^{-1.154}$ $\times$ Age (years)$^{-0.203}$ ($\times$ 0.742 if female) [12].

High-sensitivity C-reactive protein, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride concentrations were measured using AU2700 chemistry-immuno analyzer (Olympus Corporation, Tokyo, Japan). Fasting blood glucose and HbA1c were measured using HLC-723G8 analyzer (Tosoh Bioscience Inc., Tokyo, Japan).

2.2.1. CT angiography

Cardiac CT imaging was performed with a Light Speed VCT 64-slice scanner (GE Medical Systems, USA) with a slice thickness of 0.625 mm, pitch of 0.3:1, gantry rotation time of 0.2 s, Snap Shot Pulse with trigger point of 75% RR, and padding of 0–100 ms. All patients with a heart rate >65 bpm received β-blockers (propranolol, 5–20 mg i.v.) 5–10 min prior to CT scan for a goal heart rate of 55–65 bpm. Coronary calcium was evaluated by precontrast scan with ECG gating using Snap Shot Pulse with trigger point of 75% RR and padding of 0 ms. Contrast medium (Omnipaque 350; Daiichi Pharmaceutical Co, Ltd., Tokyo, Japan) dosed at 0.4–0.7 ml/kg body weight with a 40 ml saline chaser was used with DUAL SHOT (Nemoto Kyorindo Co. Ltd., Tokyo, Japan) targeting 300–400 HU of attenuation at the proximal coronary artery. For post-processing, images were sent to a dedicated Advantage Workstation 4.3 (GE Medical Systems, USA).

2.2.2. CTCA analysis

Axial images and curved multiplanar reformations were used for the evaluation of coronary artery stenosis and plaque. Two expert cardiologists, blinded to the clinical data, assessed all CTCA scans; left main, left anterior descending, left circumflex, and right coronary artery, including side branches $\geq$1.5 mm, were evaluated for stenosis using the 17-segment model recommended by ACC/AHA/ASNC [13]. In cases of disagreement between reviewers, a joint reading was carried out and consensus reached. Interpretable segments were evaluated for the presence of any atherosclerotic plaque as well as for the presence of significant coronary stenosis. Coronary plaques were defined as structures >1 mm^2 within and/or adjacent to the coronary artery lumen that could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue [14]. Coronary plaques were classified as either calcified or noncalcified. Any plaque with higher CT attenuation values than the contrast-enhanced coronary lumen or high-density CT attenuation values >130 HU at precontrast scan was defined as calcified. Any plaque that could be assigned to the coronary artery wall with CT attenuation values below the contrast-enhanced coronary lumen was defined as noncalcified [15]. A maximum of one coronary plaque was allowed per coronary segment. If both calcified and noncalcified plaques were identified in the same segment, plaques were visually assessed and then classified as that which covered a larger area. If plaques were of equal size, the segment was classified to both calcified and noncalcified categories. Regarding the assessment of obstructive lesions, all segments with plaques were evaluated using a threshold of 50% luminal narrowing on at least 2 different image planes, 1 parallel and 1 perpendicular to the vessel centerline. For each patient, the total number of segments with each type of plaque was calculated. Patients without coronary artery calcium or coronary plaques on CTCA were considered normal; abnormal was defined as having at least 1 coronary plaque. The coronary calcium score was assessed with dedicated software (Smart Score-GE Medical Systems, USA). The total calcium burden in the coronary arteries was quantified based on the scoring algorithm proposed by Agatston et al. [16].

2.3. Statistical analysis

Cystatin C concentrations were categorized into quartiles. Differences in baseline characteristics were compared with ANOVA or the Kruskal–Wallis test for continuous variables and the χ^2 test or Fisher exact test for categorical variables, as appropriate, with subsequent multilinear regression and logistic regression analysis. The outcome for multilinear regression analysis was serum cystatin C