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Original article

Prognostic impact of concurrence of metabolic syndrome and chronic kidney disease in patients undergoing coronary intervention: Involvement of coronary plaque composition

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ABSTRACT

Background and purpose: Metabolic syndrome (MetS) and chronic kidney disease (CKD) have both been reported as risk factors for cardiovascular events. The aim of this study was to assess the synergistic effect of MetS and CKD on atherosclerotic plaque and cardiovascular outcomes.
Methods and subjects: A total of 545 consecutive patients who underwent percutaneous coronary intervention (PCI) were divided into 4 groups based on the presence or absence of MetS and CKD. MetS was defined using the criteria of the Adult Treatment Panel III of the US National Cholesterol Education Program. CKD was defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2. We analyzed the incidence of major adverse cardiac events (MACE), including cardiovascular death, nonfatal myocardial infarction, target lesion revascularization, and revascularization for new lesions. We also assessed coronary plaque characteristics of 204 patients using integrated backscatter intravascular ultrasound (IB-IVUS).
Results: MACE occurred more frequently in patients with both MetS and CKD (51.4%) than in the other groups, during the follow-up period (log-rank $p < 0.001$). In the IB-IVUS analyses, patients with both MetS and CKD exhibited greater plaque burden ($p = 0.003$) with higher lipid content ($p = 0.048$) compared to the other groups. In Cox analysis, both MetS and CKD proved to be independent predictors of MACE even after adjustment for confounding factors ($p = 0.018$).
Conclusions: Comorbidity of MetS and CKD is an independent predictor of adverse cardiovascular outcomes in patients undergoing coronary intervention, an effect that may be attributed to coronary plaque instability.

Introduction

Metabolic syndrome (MetS) [1–4] and chronic kidney disease (CKD) [5–8] have been reported to be risk factors for cardiovascular events, and MetS per se has been shown to be a significant risk factor for the development of CKD [9,10]. Few studies, however, have examined the relevance of concurrence of MetS and CKD for future events. Assessing the consequences of coexistence of these clinical conditions for future adverse events is important from a prevention perspective.

Coronary atherosclerosis is the leading cause of morbidity and mortality in patients with coronary heart disease. Several risk factors are associated with severity of coronary atherosclerosis, thereby resulting in a higher incidence of cardiovascular events. The recently developed integrated backscatter intravascular ultrasound (IB-IVUS) allows the analysis of tissue components of coronary plaque in vivo, and provides helpful information for the prediction and prevention of future coronary events [11–15].

In the present study, we assessed the prognostic impact of concurrence of MetS and CKD in patients undergoing coronary

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intervention, taking into account coronary plaque morphology revealed by IB-IVUS.

Subjects and methods

Subjects

This study was a prospectively planned observational investigation of 550 consecutive patients who underwent percutaneous coronary intervention (PCI) for acute coronary syndrome and stable angina pectoris between October 2005 and March 2008 in Chubu Rosai Hospital. Of these, 4 patients were lost to follow-up and excluded. A total of 546 patients were included and divided into 4 groups based on the presence or absence of MetS and CKD as follows: (1) MetS (−) CKD (−), $n = 89$; (2) MetS (−) CKD (+), $n = 48$; (3) MetS (+) CKD (−), $n = 224$; and (4) MetS (+) CKD (+), $n = 185$. Acute coronary syndrome included ST-segment elevation acute myocardial infarction (STEMI), non-ST segment elevation acute myocardial infarction (NSTEMI), and unstable angina pectoris. The diagnosis of STEMI was based on the development of symptoms suggestive of MI, accompanied by an elevation in biomarker [creatine kinase (CK), CK-MB, or troponin T] levels of at least 2-fold higher than normal, or new significant Q waves in 2 or more contiguous leads [16]. The diagnosis of NSTEMI was based on elevation of at least 1 positive biomarker, characteristic electrocardiogram changes, and a history of prolonged acute chest pain without ST segment elevation. Unstable angina pectoris was defined as either angina with a progressive crescendo pattern or angina that occurred at rest. We assessed coronary plaque characteristics using IB-IVUS data. Patients who underwent balloon angioplasty and/or angioplasty with atherectomy before conducting IVUS and patients with STEMI or NSTEMI were excluded from IB-IVUS analyses. Then, IB-IVUS images were available in 204 consecutive patients and were divided into 4 groups as follows: (1) MetS (−) CKD (−), $n = 50$; (2) MetS (−) CKD (+), $n = 35$; (3) MetS (+) CKD (−), $n = 67$; and (4) MetS (+) CKD (+), $n = 52$.

Various lipid and inflammatory profiles were measured using commercial radioimmunoassay kits and specific immunoradiometric assays. For this purpose, blood samples were collected before PCI.

This study was approved by the ethics committee of Chubu Rosai Hospital, and all patients provided informed consent.

Definitions of MetS and CKD

MetS was defined by the criteria of the Adult Treatment Panel III of the US National Cholesterol Education Program [17]. MetS was defined as the presence of 3 or more of the following criteria: (1) Waist circumference ≥90 cm in women or ≥85 cm in men; (2) high-density lipoprotein cholesterol <50 mg/dl in women or <40 mg/dl in men; (3) serum triglycerides ≥150 mg/dl; (4) known hypertension or blood pressure ≥130/85 mmHg; and (5) fasting glucose ≥100 mg/dl. The cutoff values for waist circumference were the values used in Japanese populations [18]. Diabetes mellitus was defined as the use of any antihyperglycemic medication and was counted as meeting the glucose baseline. Glomerular filtration rate (GFR) was estimated using the simplified modification of the Diet in Renal Disease Study equation [19]. In this study, CKD was defined as an estimated GFR of <60 ml/min/1.73 m^2.

Endpoints

The primary endpoint was a major adverse cardiac event (MACE) after PCI procedure, including cardiovascular death or nonfatal MI, and any revascularization, including target lesion revascularization (TLR) and revascularization for a new lesion. The target lesion was considered as the area covered by the stent plus 5-mm margins proximal and distal to the edges of the stent. The protocol recommended that multiple interventions for lesions indicated for treatment at baseline should be performed within 30 days after the initial session. Therefore, planned revascularizations were excluded, but not unplanned revascularization or other non-target events within 30 days. Any repeat revascularization, including TLR and revascularization for a new lesion, were driven by clinical findings (presence of ischemic symptoms with a positive functional ischemia assessment or with an ischemic electrocardiogram change). To avoid "oculostenotic"procedures, revascularization for which ischemia was not proved (asymptomatic or negative functional tests) was excluded. The events were assessed by investigators blinded to the clinical data and IVUS baseline results. For multiple occurrences of the same type of event, the time to the first event was considered as the time when an endpoint was reached.

Coronary angiography and intravascular ultrasound procedure

Before performing coronary angiography and PCI, patients were given an intracoronary dose of 0.5 mg isosorbide dinitrate to prevent coronary spasm. In quantitative coronary angiography, reference diameter and percent diameter stenosis were measured by a validated automated edge-detection program (CMS-MEDIS Medical Imaging System, Leiden, The Netherlands). IVUS catheters (40 MHz) were inserted in target vessels as far as possible from the index PCI procedure. Continuous ultrasound imaging was performed during withdrawal of the catheter at a constant rate of 0.5 mm/s.

Measurements of conventional and IB-IVUS parameters

Conventional and IB-IVUS parameters were measured at locations with the worst plaque (plaque burden >40% in at least 3 consecutive frames) within the first 35 mm of the left anterior descending and left circumflex arteries, and in the worst plaque that could be observed by IVUS of the right coronary artery. For conventional IVUS analysis, two-dimensional images were quantified for lumen cross-sectional area (LCSA), external elastic membrane (EEM), cross-sectional area (CSA), and plaque + media (P + M) CSA (P + M CSA = EEM CSA − LCSA) using the IVUS system software. Eccentricity index of P + M was calculated as follows: (maximum P + M thickness − minimum P + M thickness)/(maximum P + M thickness). Remodeling index was defined as the ratio of EEM CSA at the measured lesion (minimum luminal site) to reference EEM CSA (average of the proximal and distal reference segments). The eccentricity index and the remodeling index were calculated in the segment with minimal luminal area. Three-dimensional analysis for conventional IVUS images was performed to compute vessel volume, lumen volume, and plaque volume (sum of EEM CSA, LCSA, and P + M CSA at 1-mm axial intervals for the analysis segments).

IB-IVUS analysis was performed as previously reported [11,12,20]. In brief, a personal computer equipped with custom software (IB-IVUS, YD Co., Nara, Japan) was connected to the IVUS imaging system (Clear View, Boston Scientific, Natick, MA, USA) to obtain radiofrequency signal trigger output. Ultrasound backscattered signals were acquired using a 40-MHz (motorized pullback 1 mm/s) mechanically rotating IVUS catheter, to be digitized and subjected to spectral analysis. Integrated backscatter values for each tissue component were calculated as an average power using a fast Fourier transform, measured in decibels, of the frequency component of backscattered signal from a small volume of tissue [11,12]. Segmentation of each tissue component was entirely automated. Excellent correlation of IB-IVUS and