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Diabetes exacerbates angiographic coronary lesion progression in subjects with metabolic syndrome independent of CRP levels

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Abstract

Background: Metabolic syndrome is gaining more attention as a special cluster of cardiovascular risks. However, its role, with or without diabetes, in predicting atherosclerosis progression, remains largely undetermined. We investigated the predictors for angiographic coronary atherosclerosis progression in patients with metabolic syndrome and angina pectoris.
Methods: Patients with metabolic syndrome and angina pectoris who underwent repeat coronary angiograms and had serum samples at the time of first catheterization were enrolled for analysis ($N=113$). A modified Gensini scoring system was used to define CAD progression between the index and follow-up angiograms. Those who had significant angiographic progression of coronary disease were classified as the progression group ($N=42$) and those who did not as the non-progression group ($N=71$).
Results: There were more cases of diabetes mellitus (52% vs. 31%, $p=0.040$) in the CAD progression group. The progression group also had higher baseline fasting blood glucose (150±73 vs. 117±46 mg/dl, $p=0.010$) but similar LDL cholesterol (114±38 vs. 109±33 mg/dl, $p=0.421$) than the non-progression group. In terms of inflammatory markers, there was no difference in hs-CRP ($p=0.208$), MCP-1 ($p=0.514$), or sCD40L ($p=0.549$) between the groups. In binary logistic regression, diabetes mellitus remained a significant predictor of CAD progression (OR 2.43, $p=0.030$) for patients with metabolic syndrome and angina pectoris, but hs-CRP and LDL-C were not.
Conclusion: Diabetes mellitus, but not inflammatory marker hs-CRP or LDL-C, is a significant predictor of angiographic CAD progression in patients with metabolic syndrome and angina pectoris.

Keywords: CAD progression; Metabolic syndrome; Diabetes mellitus; C-reactive protein; LDL-cholesterol; MCP-1; sCD40L

1. Introduction

Coronary artery disease (CAD) is one of the leading causes of death and imposes a great burden on healthcare worldwide. The well-documented conventional atherosclerotic risk factors include diabetes mellitus, hypertension, elevated low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), obesity, cigarette smoking and family history of premature CAD [1–4]. In recent years,

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; CAG, coronary angiogram; CI, confidence interval; ICAM-1, intercellular adhesion molecule-1; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; MCP-1, monocyte chemoattractant protein-1; P-selectin, platelet selectin; RCA, right coronary artery; sCD40L, soluble CD40 ligand; VCAM-1, vascular cell adhesion molecule-1.

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inflammation-related mediators have been found to have significant roles in the initiation, progression and clinical consequence of atherosclerosis [3,5]. In 2002, the National Cholesterol Education Program's Adult Treatment Panel III (ATPIII) considered metabolic syndrome as a multiplex risk factor for cardiovascular disease (CVD) and thus focused the attention of the cardiovascular communities on this clustered risk [6–8]. The prevalence of metabolic syndrome is about 5% to 20% according to the current published literature [9,10]. Victims of metabolic syndrome manifest a pro-thrombotic and pro-inflammatory state [11,12]. Metabolic syndrome is associated with higher incidence of cardiovascular diseases and events, and increased cardiovascular mortality [13–15]. The ten-year risk for CVD in men with metabolic syndrome generally ranged from 10% to 20% in ATP III report [6]. However, to date, few studies have investigated the predictors of chronological coronary atherosclerosis progression in patients with metabolic syndrome and angina pectoris based on coronary angiogram data [16]. Using our coronary angiographic database, we conducted this retrospective study to investigate the predictors for CAD progression in patients with metabolic syndrome.

2. Materials and methods

2.1. Study population

A cardiac catheterization report databank has recently been established in our institute, using the hospital-information-system data stored in the mainframe, and it contains all of the angiographic report data for the past 12 y. In addition, a serum databank consisting of the data for all patients who underwent different types of cardiac catheterization and were willing to donate their blood samples for academic use was established in March 1999. This study is one of the projects using these 2 databanks to investigate unresolved and challenging cardiovascular issues.

During the study period from Mar. 1999 to Jan. 2004, a total of 11,200 coronary angiographic procedures were undertaken at the catheterization laboratories. Among them, 1566 patients received more than one procedure for various indications. Of these patients with more than 1 angiogram, 233 patients with uncomplicated stable angina were found to have adequate index (1st study) and follow-up study from the angiographic databank. Among these 233 cases, 113, who had serum samples available for analysis at the first (index) coronary angiographic study and also met the criteria of metabolic syndrome, constituted the study population. Patients with the following characteristics at the time of index procedure were excluded from the study: cardiogenic shock or cardiomyopathy with heart failure, acute infection or systemic inflammation disorders, prior coronary revascularization, severe heart failure, surgery, advanced renal insufficiency, recent cerebrovascular events, significant triple vessel disease and restenotic lesions. Those who had progression only within the original diseased vessel were excluded to avoid confusion with in-segment-restenosis following precedent interventions.

2.2. Angiographic definition

The complete coronary angiograms were reviewed and angiographic measurements were made at a workstation with software for quantitative analysis of angiograms (QCA) (Philips Inturis Suite, R2.2). Those cases with coronary angiograms showing normal or <50% diameter stenosis were classified as insignificant. Those with >50% diameter stenosis in 1 of the 3 major coronary arteries and their major branches were classified as having significant CAD. A modified Gensini score was used for evaluating the coronary severity on the baseline and follow-up angiograms [17,18]. To summarize this scoring system, 5 points were given for left main lesion, 2.5 points for proximal left anterior descending artery (LAD) or left circumflex (LCX), 1.5 point for mid-segment LAD, 1 point for distal segment of LAD, first diagonal branch, LCX obtuse marginal branch, right coronary artery (RCA) and 0.5 point for 2nd diagonal branch, LCX posterolateral branch. The severity score at follow-up angiogram was the sum of the original score at index angiogram and the newly increased score. Patients who progressed from insignificant angiogram to CAD or from documented baseline CAD to new lesion(s) in a different vessel (with severity score increment) within this five-year period were classified into the progression group. Those who had insignificant angiograms or similar CAD lesions at the index and follow-up (without severity score increment) were classified into the non-progression group.

2.3. Definition of metabolic syndrome and diabetes mellitus

Metabolic syndrome was defined according to the ATP III report with modification of waist criterion into body mass index (BMI) >25 kg/m^2. High blood pressure criterion was defined as systole pressure ≥130 mmHg or diastole pressure ≥85 mmHg after multiple measurements in sitting position at rest or patients already on anti-hypertensive medication. The impaired fasting glucose was defined by fasting blood sugar ≥110 mg/dl on two occasions or patients already on oral hypoglycemic agents or insulin shots. The low HDL-C was defined as <40 mg/dl in men or <50 mg/dl in women. Hypertriglyceridemia was defined as fasting triglycerides ≥150 mg/dl. Those who met ≥3 of the above criteria were classified as having metabolic syndrome. Diabetes mellitus was defined by fasting blood glucose ≥126 mg/dl on 2 occasions or patients already on oral hypoglycemic agents or insulin shots.

2.4. Fasting blood glucose, lipid profile, hs-CRP and inflammatory markers measurements

All serum samples were stored at −70 °C till use. These blood samples were drawn from the antecubital vein from 7:00 AM to 8:00 AM after overnight fasting and before angiographic procedures. The adequately sized aliquots of serum samples of all enrolled patients were thawed and analyzed in a single batch for blood sugar, lipid profiles and inflammatory markers. Serum triglycerides and total cholesterol concentrations were assayed by an enzymatic method using commercial kits (Wako, Tokyo, Japan). The HDL cholesterol level was determined in the supernatant of plasma after magnesium chloride-phosphotungstic precipitation of apolipoprotein B-containing lipoproteins. The LDL-cholesterol concentration was estimated by the formula of Friedewald et al. [19]. Serum hs-CRP was determined by particle-enhanced immunoturbidimetry (Latex micro-particles sensitized with duck anti-CRP IgY kit, provided by Good Biotech Corp., Taichung, Taiwan). Serum sCD40L, MCP-1, ICAM-1, VCAM-1, and P-Selectin were all measured by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Inc., Minneapolis, MN).

2.5. Statistical analysis

Continuous variables are expressed as mean±SD and categorical data as percentages. Differences in continuous variables between progression and non-progression groups were assessed by the Student's *t*-test or Mann–Whitney *U* test as deemed appropriate. Categorical variables were compared by the χ^2 test with or without Yate's correction as indicated. Multivariate binary logistic regression analysis was used to test independent predictors for CAD progression. hs-CRP value tertiles were used in multivariate binary logistic regression analysis. The upper boundary of the lowest tertile was 0.085 mg/dl, and the lower boundary of the highest tertile was 0.338 mg/dl in this study. The SPSS 12.1 statistical software package (SPSS, Inc., Chicago, IL) was used for all calculations. A 2-tailed $p<0.05$ was considered statistically significant.

3. Results

3.1. Baseline demographic data

The baseline demographic data are listed in Table 1. Patient age was similar between CAD progression and non-progression groups (65±12 and 66±9 years, $p=0.525$). Among the conventional risk factors, there was no difference in hypertension