Impact of Metabolic Syndrome on 10-Year Clinical Outcomes Among Patients With Acute Coronary Syndrome

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Background: Metabolic syndrome (MetS) is a risk factor and prognosticator for ischemic heart disease, but its actual effect on long-term mortality after acute coronary syndrome (ACS) remains unknown.

Methods and Results: All-cause death and cardiovascular death were investigated among patients with ACS upon admission who underwent complete revascularization by either percutaneous coronary intervention or bypass surgery between 1984 and 1992. MetS was defined according to the NCEP/ATPIII criteria modified for waist circumference. From among 1,836 patients who underwent complete revascularization during the study period, 384 (21.0%) with ACS were enrolled, of whom 163 (42.5%) had MetS. During a mean follow-up of 10.4±3.4 years, the total number of deaths was 83 (21.6%), of which 38 (9.9%) were from cardiovascular causes. Cox proportional hazard analysis revealed that MetS increased the risk of mortality by a ratio of 1.62 (95% confidence interval [CI] 1.01–2.59, P=0.046) and of cardiovascular death by 2.40 (95% CI 1.16–4.94, P=0.018) in patients with ACS.

Conclusions: MetS is a powerful determinant of long-term all-cause and cardiovascular death after ACS. Furthermore, MetS and ACS might jointly exacerbate poor long-term outcomes. (Circ J 2009; 73: 1454–1458)

Key Words: Acute coronary syndrome; Long-term mortality; Metabolic syndrome; Revascularization

Metabolic syndrome (MetS) is a cluster of cardiovascular disease risk factors associated with increased morbidity and mortality and characterized by abdominal obesity, insulin resistance, dyslipidemia and hypertension. Moreover, MetS is associated with the severity of coronary artery disease (CAD) and is a prevalent and powerful risk factor for operative mortality in patients undergoing coronary artery bypass surgery (CABG). Acute coronary syndrome (ACS) is associated with higher rates of morbidity and mortality, and the risk of recurrent ischemic events is greater than after stable angina. Considerable evidence shows that MetS is highly prevalent among patients with ACS.

However, the effects of MetS on the long-term mortality of patients with ACS have not been clarified, so in present study the effect of MetS on the long-term mortality of patients with ACS after complete revascularization, including percutaneous coronary intervention (PCI) and CABG, was examined.

Methods

Patients and Data Collection

Data from consecutive patients who had undergone CABG and/or PCI at Juntendo University Hospital between January 1984 and December 1992 were retrospectively analyzed. We enrolled patients in whom complete revascularization, defined as the absence of bypassed major vessels with ≥50% stenosis, was achieved to minimize the influence of adverse outcomes related to incomplete procedures and to distinguish significant CAD from ACS that presented upon admission. We excluded patients with other known life-threatening diseases at baseline and those with associated complex cardiac procedures, such as valve replacement or aneurysm repair at the time of surgical revascularization.

ACS was identified among patients with acute myocardial infarction (AMI) or unstable angina (UAP). AMI was diagnosed based on the presence of typical chest pain with ST-segment elevation on ECG and increased serum creatine kinase levels. UAP was diagnosed based on the presence of characteristic chest pain symptoms at rest associated with transient ischemic ST-segment shifts and normal serum creatine kinase levels. All other patients were defined as not having ACS. Indications for revascularization in all patients were objective evidence of myocardial ischemia (positive stress test), ischemic symptoms or signs of ACS associated with significant angiographic stenosis.

Demographic data (including age, gender, body mass index [BMI]), coronary risk factors (blood pressure [BP], total cholesterol [TC], high-density lipoprotein-cholesterol [HDL-C], triglycerides [TG], fasting blood glucose [FBG], smoking status, family history of CAD), medication at the time of revascularization, and factors and comorbidities associated with revascularization (prior myocardial infarction [MI], prior stroke, current dialysis and atrial fibrillation [AF]) were prospectively gathered. Blood samples were obtained in the early morning after an overnight fast. BP was measured at the time of admission and for a few days thereafter. Left ventricular ejection fraction (LVEF) was...
measured in all patients by echocardiography immediately after revascularization during initial hospitalization.

Outcome data were collected by serial contact (every 5 years) with the patients or their families until September 2000. The medical records of patients who died or who were treated in Juntendo University hospital were analyzed. Other institutions where patients were admitted were asked to provide details and the causes of death. Mortality data were categorized as death from all causes or cardiovascular death, including death from CAD, stroke, cardiogenic shock, and sudden death.

Patients were categorized according to the presence or absence of MetS at baseline, using the following modified NCEP-ATPIII criteria. Obesity was defined as BMI ≥25 kg/m² according to the Japanese criteria for obesity, and applied instead of waist circumference as in the NCEP-ATPIII criteria. The other MetS criteria were the same as those defined by NCEP-ATPIII: TG ≥150 mg/dl; HDL-C <40 mg/dl for men, <50 mg/dl for women; BP ≥130/85 mmHg and FBG ≥100 mg/dl, which is currently recommended instead of the previous value of ≥110 mg/dl. Patients with 3 of these 5 criteria were regarded as having MetS. Patients with BP ≥140/90 mmHg or taking angiotensin-converting enzyme inhibitors (ACEI), calcium-channel blockers (dihydropyridines) or β-blockers were regarded as having hypertension and those with FBG ≥126 mg/dl or taking oral hypoglycemic agents or injectable insulin were regarded as having diabetes mellitus (DM).

The hospital’s internal review board approved this study, which was performed according to the institutional ethics policies.

### Statistical Analysis
Continuous variables are expressed as means ± SD and were compared using t-test. Categorical data were tabulated as frequencies and percentages and compared using the chi-square test or Fisher’s exact test. Kaplan-Meier estimation with a log-rank test comprised the unadjusted analysis.
We applied multivariate Cox proportional-hazards regression to examine risks for all-cause and cardiovascular deaths in the groups with and without MetS. The hazard ratio (HR) and 95% confidence interval (CI) of MetS were computed using separate models adjusted for age, gender, BMI, DM, hypertension, TC, smoking status (defined as one who smoked at the time of the revascularization or who had quit smoking within 1 year before the procedure), prior MI, prior stroke, currently undergoing dialysis, AF, multivessel disease, LVEF and whether complete revascularization was achieved by isolated PCI. A P-value <0.05 was considered significant. All data were analyzed using SPSS version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

**Results**

**Baseline Characteristics and Prevalence of Factors**

Complete revascularization was achieved in 1,836 patients during the study period. We enrolled 384 (21.0%) of those with ACS and among them 163 (42.5%) had MetS. Baseline and clinical event data were fully documented during the follow-up period (mean 10.4±3.4 years) for all patients (Tables 1, 2). Patients with MetS had a significantly higher BMI, FBG, TG and BP, and lower HDL-C than those without MetS, as these characteristics comprise part of the definition of MetS. Most of the patients, regardless of group, were middle-aged, non-obese males who were being treated with nitrates and aspirin. Fifty (22.6%) and 37 (22.6%) of the non-MetS and MetS groups, respectively, were treated with statins. No patients in any group had been implanted with stents because all underwent PCI using only balloon angioplasty. In addition, all cardiopulmonary bypass surgery was conventional and 32.3% included an arterial graft.

**Unadjusted and Adjusted Analysis for Mortality and Cardiovascular Events**

During long-term follow-up, 83 (21.6%) of the patients with ACS died. Of them, cardiovascular mortality accounted for 45.7% (n=38). Furthermore, among all of the deceased patients, 71 (85.5%) died at Juntendo University hospital and 12 (14.4%) died elsewhere, such as at home or at other
Impact of MetS on ACS

Discussion

Our study demonstrated that MetS exacerbated long-term overall and cardiovascular mortality in patients with ACS after complete revascularization when known risk factors for cardiovascular disease were established. MetS comprises a cluster of risk factors that are powerful predictors of cardiovascular disease, and synergistic interactions among them cause or accelerate atherosclerotic progression. Furthermore, patients with MetS have impaired endothelial function and a worsened inflammatory state both of which are significantly associated with coronary lesion complexity and CAD. Patients with ACS and MetS are more susceptible to multiple complex coronary lesions, suggesting coronary plaque vulnerability. Based on these facts, we postulate that MetS exacerbates coronary lesions and causes an increase in cardiac mortality rates.

Consistent with published primary or secondary observational studies, we found worse clinical outcomes among ACS patients with, rather than without, MetS. Several other studies have also identified MetS as a powerful independent predictor of adverse outcomes in patients with ACS. Recent reports indicate that MetS is associated with 3.5-year total mortality, and congestive heart failure in patients with AMI. Another study found increased total mortality among ACS patients with, than without, MetS during a 16-month follow-up. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACLE) trial, patients with ACS and MetS had increased all-cause mortality and an increased rate of reaching the primary endpoint (death, nonfatal MI, cardiac arrest, or recurrent unstable myocardial ischemia) during a 16-week follow-up.

Our study differs from others from the following perspectives. This is the first study in which all patients were treated with complete revascularization. Furthermore, our follow-up of 10 years is considerably longer than in previous studies, and we are the first to provide such evidence in an Asian population. Our observations confirm previous findings and extend the knowledge of the clinical importance of MetS, because we investigated its long-term prognostic significance in patients with ACS treated by PCI or CABG. The longer follow-up might be important, as an apparent lag time of 5 years passed before the mortality curves with and without MetS started to diverge in our study. Consequently, previous studies might have underestimated the overall mortality risk associated with MetS because the follow-up was <5 years. The average follow-up in our study was 10.4 years, with HR values of 1.62 for all-cause death and 2.40 for cardiovascular death among patients with MetS. The HR was lower in our study than in other published studies, which might be explained by our study population, because the prognosis of Asian patients with ACS tends to be better than that of European or North American patients.

Differences in mortality between MetS and non-MetS patients can be partially explained by baseline differences. Consistent with prior primary or secondary observational studies, we found that patients with MetS and ACS had worse baseline clinical characteristics, such as a higher frequency of hypertension, diabetes, dyslipidemia and obesity. That MetS is associated with several coronary risk factors is hardly surprising, because it comprises a cluster of risk factors, each of which is a powerful predictor of cardiovascular disease. However, our results also showed that MetS remained a significant predictor of long-term mortality even after adjustment for conventional risk factors. The effect of MetS on cardiovascular events was independent of its association with DM, and the risks associated with DM and MetS were incremental. However, DM is a critical predictor of future cardiovascular events. The risk of death among patients with MetS was mainly associated with transformation in DM; these patients developed a significantly increased risk of DM during follow-up and approximately 33% of patients who develop new MI also develop abnormal glucose tolerance or diabetes within 3.5 years.

This is the first study to provide such evidence in an Oriental population over the long-term (>10 years of follow-up), and it is compatible with the results of Western randomized control studies of shorter follow-up periods. Our patients were not randomly allocated; the revascularization procedure was selected by doctors after consideration of individual peri- and post-procedural risk. Therefore, our findings might add useful and clinically relevant information to observational data generated from previous cohort studies.

Study Limitations

Firstly, we used the modified National Cholesterol Education Program criteria to diagnose MetS and assessed central obesity using BMI instead of waist circumference. We selected BMI ≥25 kg/m² as the cut-off for obesity based on the results of a study on the relationship between BMI, visceral fat area or waist circumference and obesity among Japanese. Moreover, according to the NCEP-ATPIII criteria, patients who treated with antihypertensive drugs were regarded as high the indication for drug administration for hypertension and ischemic heart disease might differ according to the era when the medicine was prescribed. Secondly, the present study was observational in nature; even though we used an adjusted analysis, other unknown confounders

Table 3. Results of Adjusted Cox Proportional Hazards Regression Analysis

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<th>Non-MetS (n=221)</th>
<th>MetS (n=163)</th>
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<tr>
<td></td>
<td>n (%) HR (95%CI)</td>
<td>n (%) HR (95%CI)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>39 (17.7) 1.00 (Reference)</td>
<td>44 (27.0) 1.62 (1.01–2.59) 0.046</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>15 (6.8) 1.00 (Reference)</td>
<td>23 (14.1) 2.40 (1.16–4.94) 0.018</td>
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HR, hazard ratio; CI, confidence interval. Other abbreviations see in Table 1.
might have affected the outcomes. Various medications used at the time of PCI/CABG surgery such as ACEI, β-blockers, calcium-channel blockers and oral hypoglycemic agents might have affected the results. However, these differences would only have led to an underestimation of the association between MetS and mortality or cardiac event rates, which would probably be because drugs that helped to reduce long-term mortality or cardiac event rates after revascularization therapy, such as ACEI and β-blockers, were administered to more patients with than without MetS at the time of PCI/CABG surgery. In addition, therapies instituted after PCI/CABG surgery might also have affected the mortality and cardiac event rates. Thirdly, we could not collect an adequate volume of data from patients regarding metabolic factors and BP throughout the course of the disease. Thus, we have been unable to determine the incidence rates of overt DM and hypertension in both groups.

Conclusions

We believe that our study is the first to verify MetS as a prognostic factor for ACS, as a literature search did not uncover any reports describing the long-term prognosis of CAD complicated by MetS. These findings suggest that the recognition of MetS is important in secondary prevention in patients with ACS.

Disclosure

No authors report any conflict of interest.

References