Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 46, No. 2, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.03.062

Metabolic Syndrome and Risk of Cardiovascular Events After Myocardial Infarction

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OBJECTIVES We aimed to assess the prevalence and prognostic role of metabolic syndrome (METS) and diabetes in post-myocardial infarction (MI) patients.

BACKGROUND Diabetes is a well known risk factor for patients with previous MI, but glycemic dysmetabolism develops over a protracted period of time. Scanty data are available on the role of METS in patients with previous MI.

METHODS Adjusted Cox's regression models, having diabetes, death, major cardiovascular events (CVE), and hospitalization for congestive heart failure (CHF) during follow-up as outcome events, were fitted on 11,323 patients with prior MI enrolled in the GISSI-Prevenzione Trial.

RESULTS At baseline, 21% and 29% of patients had diabetes mellitus and METS, respectively. The METS patients had a significant (93%) increased risk of diabetes during follow-up. As compared with control subjects, the probability of death and CVE were higher in both METS (+29%, p = 0.002; +23%, p = 0.005) and diabetic patients (+68%, p <0.0001; +47%, p <0.0001), although diabetic but not METS patients were more likely to be hospitalized for CHF (+89%, p <0.0003 and +24%, p = 0.241). Moderate (−6% to −10%) and substantial (>−10%) weight reduction were associated with a significant (18% and 41%, respectively) decreased risk of diabetes. Weight gain was significantly associated with increased risk of diabetes. The risk conferred by METS and diabetes tended to be higher among women.

CONCLUSIONS In patients with MI, METS and diabetes were highly prevalent and are associated with increased risk of death and CVE. Diabetes is also associated with increased risk of hospitalization for CHF. Weight reduction significantly decreased the risk of becoming diabetic in patients with METS. (J Am Coll Cardiol 2005;46:277–83) © 2005 by the American College of Cardiology Foundation

Type 2 diabetes mellitus is a well recognized risk factor for cardiovascular morbidity and mortality (1–5). Glucose metabolism abnormalities, however, develop over a prolonged period of time during which individuals are at high risk of cardiovascular events despite glucose levels that could be considered as normal (6–10). This period is characterized by a progressive resistance to the action of insulin, a process called insulin resistance (IR) that usually clusters with several cardiovascular risk factors (11–15). The diagnosis of IR is complex and cannot be easily performed in clinical practice (16–19); however, the metabolic syndrome (METS) is characterized by the clustering of risk factors related to IR and is considered to be an early indicator of impaired glucose metabolism (20–24). The diagnosis of METS proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) is based on simple clinical criteria (20) and is considered a prognostic indicator of vascular risk in patients with no overt coronary artery disease (20–24).

Because scanty data are available on the prognostic role of METS in patients with previous myocardial infarction (MI) (25), we analyzed the GISSI-Prevenzione Trial database (26) to assess the prevalence of METS and diabetes as well as their association with cardiovascular events in post-MI patients.

METHODS

Patients. A detailed description of the study has been reported previously (26). Briefly, 11,323 patients with recent (≤3 months, median 16 days) MI were enrolled in the GISSI-Prevenzione Trial, a multicenter open-label clinical study, with blinded validation of events and follow-up duration of 3.5 years, on the efficacy of polyunsaturated fatty acids (PUFA) (1 g daily) and vitamin E (300 mg daily). Clinical, laboratory, and instrumental evaluation of the patients recruited in the study were carried out at baseline and follow-up visits that were scheduled at 6, 12, 18, 30, and 42 months.

The outcomes measures for this analysis were: diabetes development during follow-up (defined as fasting glucose

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Manuscript received November 9, 2004; revised manuscript received March 16, 2005, accepted March 29, 2005.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
BMI	= body mass index
CHF	= congestive heart failure
CVE	= cardiovascular events
IR	= insulin resistance
METS	= metabolic syndrome
MI	= myocardial infarction
NCEP-ATP III	= National Cholesterol Education Program Adult Treatment Panel III
NYHA	= New York Heart Association
PUFA	= polyunsaturated fatty acids

≥126 mg/dl or antidiabetic treatment) in non-diabetic patients at baseline, all-cause mortality, cumulative rate of cardiovascular events (CVE) (cardiovascular death, nonfatal MI, nonfatal stroke), and development of congestive heart failure (CHF) that was assessed according to hospitalization for CHF during follow-up in patients with no heart failure at baseline.

The analysis on overall mortality and CVE was carried out in 10,384 patients (i.e., after excluding 939 patients who had missing data for METS components at baseline). For the analysis of diabetes development during follow-up, we excluded 2,139 patients with diabetes at baseline and 777 cases with no measurement of glucose levels during follow-up. The analysis on CHF hospitalizations was carried out on 8,417 patients who were free from CHF (New York Heart Association [NYHA] functional class II or physician-reported CHF) at baseline and had complete information for CHF assessment (NYHA functional class, medication report) at least at one scheduled follow-up visit.

To assess the effect of weight change on the risk of CVE and diabetes development during follow-up, 7,027 patients who had body weight measurements both at baseline and at the first follow-up visit and who were free of cardiovascular events and diabetes until the first follow-up visit were included in the analysis. We also evaluated the effect of weight change in 4,422 patients with body mass index (BMI) >25 kg/m^2. We considered patients who had no or a light decrement of body weight (<−5%) as the reference class. Body weight changes between the baseline and the first follow-up visit were defined as moderate (−6% to −10%) and substantial (>−10%) weight reductions, whereas weight increments were defined as light (≥0% to +5%), moderate (+6% to +10%), and substantial (>+10%).

For the diagnosis of METS at baseline, we modified the NCEP-ATP III criteria for abdominal obesity by using the median value of BMI ≥26 kg/m^2 instead of the waist circumference, which was not available. The cutoff for BMI at the median value was indicative of overweight, and being over the upper limit of normality, it could be considered a proxy of visceral adiposity. Accordingly, diagnosis of METS was established when non-diabetic subjects had at least three of the following five criteria: visceral adiposity (BMI ≥26 kg/m^2), high triglycerides (≥150 mg/dl), low high-density lipoprotein cholesterol (<40 mg/dl in men and <50 mg/dl in women), hypertension (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥85 mm Hg or antihypertensive treatment or history of hypertension), and impaired fasting glucose (≥110 mg/dl and <126mg/dl). For diagnosis of METS, we did a sensitivity analysis by using a BMI value of 28 and 29 kg/m^2 (corresponding to the upper quartile and upper quintile) with no substantial difference in terms of prognostic capacity of METS (data not shown). Diabetes at baseline was diagnosed if either glucose ≥126 mg/dl, patients were on anti-diabetic treatment, or physician-reported diabetes.

Statistical methods. One-way analysis of variance and chi-square test were used to test continuous and categorical variables at baseline, respectively.

Cox proportional models were fitted with all-cause mortality, CVE, late onset CHF, and new diagnosis of diabetes during follow-up as outcome measures. The following potential confounders were included in the multivariable models: 1) age and gender; 2) electrical instability (defined as ≥10 premature ventricular beats/h, sustained or repetitive arrhythmias during 24-h Holter monitoring), residual ischemia (angina pectoris, positive exercise testing), ejection fraction; 3) smoking, total cholesterol, peripheral vascular disease; and 4) n-3 PUFA, vitamin E, antiplatelet agents, angiotensin-converting enzyme (ACE) inhibitors, statins, and beta-blockers. The multivariate model that was aimed at assessing the effect of weight reduction on risk of late onset diabetes also included BMI levels measured at baseline. Cox proportional hazards event-free survival curves, adjusted for covariates means, were plotted. All probability values are two-sided. All computations used the SAS statistical package (SAS Institute Inc., Cary, North Carolina).

RESULTS

Baseline descriptive statistics. Out of a total of 10,384 patients, 2,139 (20.6%) had diabetes mellitus and 3,047 (29.3%) had METS (Table 1). As compared with METS and control subjects, diabetic patients were more likely to be female, older, and with higher prevalence of peripheral artery disease and MI before the index event leading to recruitment into the study. Diabetic patients were also more likely to have an impaired left ventricular function with lower levels of ejection fraction and higher prevalence of NYHA functional class II. As to medication use, diabetic patients were more likely to receive ACE inhibitors and less likely to be given aspirin and beta-blockers (Table 1).

Normal and METS patients were much more similar, the latter group having a higher prevalence of women (12.3% vs. 15.4%, $p < 0.0001$) and of use of beta-blockers, ACE inhibitors, and aspirin (Table 1).

There were some minor differences at baseline between patients who were included in the analysis and those who