Prevalence and Impact of Metabolic Syndrome on Hospital Outcomes in Acute Myocardial Infarction

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Background: The impact of metabolic syndrome after acute myocardial infarction (AMI) has not yet been studied. In a population-based sample of patients with AMI, we sought to determine the prevalence of metabolic syndrome in patients with AMI, its impact on hospital outcomes, and to assess the relative influence of each of the components of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III definition of metabolic syndrome on the risk of death and heart failure.

Methods: A total of 633 unselected, consecutive patients hospitalized with AMI were categorized according to the NCEP ATP III metabolic syndrome criteria (presence of ≥3 of the following: hyperglycemia; triglyceride level ≥150 mg/dL [≥1.7 mmol/L]; high-density lipoprotein cholesterol level <40 mg/dL [<1.04 mmol/L] in men and <50 mg/dL [<1.30 mmol/L] in women; blood pressure ≥130/85 mm Hg; and waist circumference >102 cm in men or 88 cm in women).

Results: Among the 633 patients, 290 (46%) fulfilled the criteria for metabolic syndrome. Patients with metabolic syndrome were older and more likely to be women. Acute myocardial infarction characteristics and left ventricular ejection fraction rates were similar for both groups. In-hospital case fatality was higher in patients with metabolic syndrome compared with those without, as was the incidence of severe heart failure (Killip class >II). In multivariate analysis, metabolic syndrome was a strong and independent predictor of severe heart failure, but not in-hospital death. Analysis of the predictive value of each of the 5 metabolic syndrome components for severe heart failure showed that hyperglycemia was the main correlate of the risk of development of severe heart failure during AMI.

Conclusions: In an unselected population of patients with AMI, the prevalence of metabolic syndrome was high. Metabolic syndrome appeared associated with worse inhospital outcome, with a higher risk of development of severe heart failure. Among metabolic syndrome components, hyperglycemia was the main correlate of the risk of development of severe heart failure during AMI.

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METABOLIC SYNDROME, also referred to as insulin resistance syndrome, is a cluster of risk factors in an individual that may precede type 2 diabetes mellitus.1,2 It is also associated with an increased risk of cardiovascular disease.3 In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III provided a new definition for metabolic syndrome.4 The definition incorporates thresholds for the following 5 variables: waist circumference; concentrations of triglycerides, high-density lipoprotein (HDL) cholesterol, and fasting plasma glucose; and blood pressure. A classification of metabolic syndrome is triggered when predefined limits of any 3 of these 5 criteria are exceeded. Based on these criteria, an analysis of data on 8814 men and women aged 20 years or older from the Third National Health and Nutrition Examination Survey, a cross-sectional health survey of a nationally representative sample of the US population, found that the prevalence of metabolic syndrome was 25% among white Americans and 44% among those 50 years and older.5

Studies based on populations at high risk for cardiovascular disease have shown a very high prevalence of metabolic syndrome. In patients with hypertension or type 2 diabetes mellitus, the prevalence of metabolic syndrome ranges from 35% to 80%.6,7 In a cohort of 1108 symptomatic patients of French and Canadian origin who underwent elective coronary angiog...
The design and methods of the population-based Observatoire des Infarctus de Côte-d’Or Survey have been published. Briefly, since January 1, 2001, the Survey’s registry has been collecting in-hospital data from patients hospitalized with AMI in the 6 public and private hospitals of Côte-d’Or, a French region with a population of approximately 500,000 inhabitants. These hospitals represent all 3 of the cardiology and all 3 of the coronary care units of the region.

Data were collected at each site by a study coordinator (M.Z., I.L., J.-C.B., A.O., and Y.C.) trained in completing the core record form and extracting data from medical records, using a standardized case report form. Cases were ascertained by prospective collection of consecutive admissions. Internal and external audit checks are performed every year, and show that less than 1% of patients might have been missed by the collection procedure. Standardized definitions for myocardial infarction (MI) and patient-related variables and clinical outcomes were used. Patients were enrolled in the registry if they were 18 years or older and were admitted to participating hospitals within 24 hours of the onset of symptoms with a suspected diagnosis of MI. A final diagnosis of MI was made in the presence of serial increases in serum biochemical markers of cardiac necrosis, associated with typical electrocardiographic changes and/or typical symptoms as defined by the Joint Committee of the European Society of Cardiology and the American College of Cardiology. Patients with ST-segment elevation or new or suspected new left bundle branch block on the admission electrocardiogram were defined as having ST-segment elevation MI (STEMI). The remaining patients were categorized as having non-STEMI. The study complied with the Declaration of Helsinki and was approved by the ethics committee of the Centre Hospitalier Universitaire de Dijon, Dijon, France. Each patient gave written informed consent before participation. The consent form was signed by relatives of patients who were unable to sign the form. Failure to obtain a signed consent form rendered that patient ineligible for inclusion in the registry.

DEFINITION OF HEART FAILURE

Patients with diabetes are at increased risk of heart failure after MI, so we analyzed the impact of metabolic syndrome on the development of heart failure. Heart failure was defined as the highest Killip class reached during hospitalization. Severe heart failure was defined as Killip class greater than II. Cardiogenic shock was defined as a systolic blood pressure less than 90 mm Hg, persisting for longer than 1 hour despite fluid challenge and associated with clinical signs of hypoperfusion.

BIODILIGE VARIABLES

Blood samples were drawn at admission (for levels of highsensitivity C-reactive protein, serum creatinine, and blood glucose), the following morning (fasting sample for levels of glycosylated hemoglobin, triglycerides, and HDL cholesterol), and at days 4 and 5 (fasting sample for determination of blood glucose level, as described by Norhammar et al). Fasting glycemia was determined from the mean blood glucose values at days 4 and 5. Peak creatine kinase levels during the in-hospital stay were also measured. Creatinine clearance was estimated using the Cockcroft-Gault formula.

DEFINITION OF METABOLIC SYNDROME

Metabolic syndrome was defined according to the NCEP ATP III criteria. Patients received a diagnosis of metabolic syndrome if they had any 3 of the following 5 criteria: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), high triglyceride levels (>150 mg/dL [≥1.7 mmol/L]), low HDL cholesterol levels (<40 mg/dL [<1.04 mmol/L] in men and <50 mg/dL [<1.3 mmol/L] in women), hyperglycemia (history of diagnosed diabetes mellitus or fasting blood glucose level ≥110 mg/dL [≥6.1 mmol/L]), and high blood pressure (treated hypertension, systolic blood pressure ≥130 mm Hg, or diastolic blood pressure ≥85 mm Hg).
RESULTS

CHARACTERISTICS

From January 1, 2001, to April 14, 2004, 811 consecutive patients underwent screening; of these, 178 had an unconfirmed diagnosis of AMI (n=155) or failed to provide a signed informed consent form (n=23). Among the patients who failed to provide informed consent, further analysis showed that their baseline and outcome characteristics were similar to those of our study population for age (P=.56), sex (P=.23) and in-hospital case fatality (P=.78). Thus, 633 patients with a confirmed diagnosis of MI were enrolled in the registry. Among these patients, 290 (46%) had metabolic syndrome according to the NCEP ATP III criteria. The prevalence of components of metabolic syndrome in both patient populations is shown in the Figure. The clinical characteristics of the study population are shown in Table 1. Patients with metabolic syndrome were older, more likely to be women, had a higher number of cardiovascular risk factors, and had a more frequent history of previous MI than patients without metabolic syndrome. Moreover, the delay from onset of symptoms to hospital admission was longer in patients with metabolic syndrome, and there was a higher incidence of heart failure on admission (Killip class >1). In the subset who underwent echocardiography (444 [70%]), LVEF was similar for both groups. Patients with metabolic syndrome were less likely to receive thrombolytic therapy. Median plasma C-reactive protein levels were markedly higher in patients with metabolic syndrome compared with those without the syndrome (Table 2). For patients with metabolic syndrome, creatinine clearance was significantly lower, glucose and lipid profiles were markedly abnormal (Table 2), and levels of LDL cholesterol were lower.

CARDIAC EVENTS

The in-hospital case fatality rate among patients with metabolic syndrome was more than twice that of patients without the syndrome (Table 3). Moreover, overt heart failure (Killip class >1) or severe heart failure (Killip class >II) developed in patients with metabolic syndrome during hospitalization more frequently than in patients without the syndrome. Other outcome events occurred with a similar frequency in both groups.

PREDICTORS OF EVENTS

Results of multivariate analysis demonstrated that metabolic syndrome was not an independent predictor for case fatality when adjusted for age, female sex, creatinine clearance, STEMI, anterior wall MI, smoking, admission pulse, systolic and diastolic blood pressures, previous MI, and metabolic syndrome as predictors of cardiovascular death. These variables were chosen because they have been shown to account for a large proportion of the prognostic information in the setting of acute coronary syndrome.18 suggesting that treatment variables provide only poor prognostic information, and were included in stepwise regression analyses. For the other models, baseline characteristics (eg, age, history of MI, history of smoking, female sex, anterior wall MI, creatinine clearance, admission pulse, and systolic and diastolic blood pressures)19 and individual metabolic syndrome components were tested in a backward stepwise regression analysis as predictors for development of severe heart failure or cardiogenic shock. Creatinine clearance of 60 mL/min or less was defined as severe renal dysfunction.20 We performed the $\chi^2$ test to test for significance. Adjusted odds ratios (ORs) with accompanying 95% confidence intervals (CIs) were reported. We used the risk ratio with 95% CI to evaluate the association between each component of metabolic syndrome and outcome.21

Diabetes mellitus and impaired fasting glucose level were defined according to revised American Diabetes Association definitions.17 Patients were classified as having diabetes if they had a history of diagnosed diabetes mellitus or if their mean fasting blood glucose level was at least 126 mg/dL (7.0 mmol/L). Impaired fasting glucose level was defined as a mean fasting glucose level ranging from 110 mg/dL (6.1 mmol/L) to 126 mg/dL (7.0 mmol/L), and fasting glucose level within the reference range was defined as a mean fasting glucose level less than 110 mg/dL (<6.1 mmol/L).

STATISTICAL ANALYSIS

Continuous data were expressed as medians and interquartile ranges or means±SD, as appropriate, and dichotomous data were expressed as percentages. We performed a Kolmogorov-Smirnov analysis for continuous variables to test for normality. We performed comparisons between groups by unpaired $t$ test (LVEF and low-density lipoprotein [LDL] cholesterol level) or the nonparametric Mann-Whitney test as appropriate. We analyzed categorical data by the $\chi^2$ test.

A multiple logistic regression model was performed to examine the association between the metabolic syndrome and adverse hospital events. The first model included age, female sex, creatinine clearance, STEMI (as opposed to non-STEMI), anterior wall MI, smoking, admission pulse, systolic and diastolic blood pressures, previous MI, and metabolic syndrome as predictors of cardiovascular death. These variables were chosen because they have been shown to account for a large proportion of the prognostic information in the setting of acute coronary syndrome.18 suggesting that treatment variables provide only poor prognostic information, and were included in stepwise regression analyses. For the other models, baseline characteristics (eg, age, history of MI, history of smoking, female sex, anterior wall MI, creatinine clearance, admission pulse, and systolic and diastolic blood pressures)19 and individual metabolic syndrome components were tested in a backward stepwise regression analysis as predictors for development of severe heart failure or cardiogenic shock. Creatinine clearance of 60 mL/min or less was defined as severe renal dysfunction.20 We performed the $\chi^2$ test to test for significance. Adjusted odds ratios (ORs) with accompanying 95% confidence intervals (CIs) were reported. We used the risk ratio with 95% CI to evaluate the association between each component of metabolic syndrome and outcome.21

Figure. Prevalence of individual components of metabolic syndrome in patients with and without metabolic syndrome. HDL indicates high-density lipoprotein.
ing, and creatinine clearance [OR, 2.13; 95% CI, 1.28-3.57; P = .003]. Analysis of the association between individual components of metabolic syndrome and the risk of development of severe heart failure showed that hypoglycemia and low HDL cholesterol level had the strongest association with severe heart failure (Table 4). Among the 5 criteria for metabolic syndrome, only hypoglycemia was an independent determinant for the prediction of cardiogenic shock, even when adjusted for age, female sex, previous MI, anterior wall MI, creatinine clearance, and the other components of metabolic syndrome. Hyperglycemia, as part of the metabolic syndrome criteria, was a strong and independent predictor of severe heart failure (Table 5).

**COMMENT**

In this population-based registry of patients with MI, metabolic syndrome, defined per the NCEP ATP III criteria, appears to be extremely frequent, associated with worse in-hospital outcome, and characterized by a higher risk of development of heart failure. Among the individual components of metabolic syndrome, hypoglycemia appears the main determinant of this increased risk of development of heart failure.

**PREVALENCE AND CHARACTERISTICS OF METABOLIC SYNDROME**

Only a few studies have evaluated the prevalence of metabolic syndrome, as defined by the NCEP ATP III criteria, in patients with symptomatic arterial disease. In 1108 patients of French Canadian origin with symptoms of coronary artery disease, it has been shown that the syndrome is present in 51% of the patients and that the number of its metabolic features increases with the severity of angiographic coronary artery disease. Moreover, in patients with coronary heart disease, peripheral arterial disease, or abdominal aortic aneurysm, an increase in the number of components of the metabolic syndrome was associated with an increase in mean carotid intima media thickness (P < .001) and a decrease in ankle brachial pressure index (P < .01).

These findings suggest that metabolic syndrome, as defined by the NCEP ATP III criteria, is very common among patients with coronary artery disease, because almost 1 in 2 patients had metabolic syndrome and that it is associated with advanced vascular damage. Our study, based on an unselected population of patients hospitalized with MI, confirms the high prevalence of metabolic syndrome in patients with arterial disease and extends...
METABOLIC SYNDROME AND PROGNOSIS

Metabolic syndrome was associated with an increased case-fatality rate. However, after adjustment for the major determinants of mortality in AMI, metabolic syndrome was no longer an independent predictor of case fatality, possibly because of the lack of power in our relatively limited sample. These findings may reflect the substantially worse baseline characteristics of patients with, compared with those without, metabolic syndrome. Moreover, in this cohort of patients with AMI, metabolic syndrome did not appear to have an impact on the risk of ventricular tachyarrhythmia or recurrent MI. However, there was a consistent and marked increase in the incidence of heart failure and cardiogenic shock in patients with metabolic syndrome. The strong association between metabolic syndrome and the occurrence of severe heart failure remained highly significant, even after adjustment for confounding factors. We also observed a trend for a lower median level of peak plasma creatine kinase, which is inconsistent with the worse in-hospital outcome found in this group. This finding could be the result of the more frequent early deaths in patients with metabolic syndrome leading to a truncation of the peak creatine kinase value (the lack of difference in LVEF between patients with vs without the metabolic syndrome would support this hypothesis), or it may be related to the fact that the peak creatine kinase value is a poor reflection of infarct size.

More advanced vascular damage has been associated with the presence of metabolic syndrome in patients with manifest vascular disease, which may worsen the prognosis. Metabolic syndrome represents a cluster of several risk factors, each of which may be involved in this poor outcome. The presence of hypertension was not a major determinant for mortality in our study population; these data are in agreement with previous studies that showed that hypertension is only a moderate predictor of death at long-term follow-up after MI. Likewise, low HDL cholesterol and elevated triglyceride levels appeared to have little impact on hospital outcomes, confirming the data from the Aspirin Myocardial Infarction Study. Although abdomi-
nal obesity undoubtedly plays an important role in disease evolution and represents a valid early marker of individuals at high risk of abnormal glucose metabolism. Moreover, in studies evaluating the biological relevance of lipoprotein assessment at the acute phase of MI, a gradual decrease in mean HDL cholesterol and triglyceride levels during the in-hospital stay has been reported but is only minor during the first 24 hours. This decrease could therefore only weakly influence the calculation of the prevalence of metabolic syndrome. Second, although we assessed risk factors at the time of the index event, we cannot reliably measure how long the risk factors had been present before the MI. The need for written informed consent may have resulted in the lack of enrollment of dying, unconscious, or intubated patients, and therefore may have resulted in enrollment bias toward lower risk among patients with MI. Furthermore, the in-hospital case fatality rate observed in our study population, which is very similar to the case fatality rates reported in current registries of acute MI, suggests that this potential bias had little impact on our results.

CONCLUSIONS

To our knowledge, this is the first prospective study to describe the prevalence of metabolic syndrome in AMI and to assess its impact on hospital outcomes. Our study showed the high prevalence of metabolic syndrome among patients with AMI and highlights the detrimental impact of metabolic syndrome on short-term outcomes, particularly heart failure. Finally, our study suggests that, among metabolic syndrome components, hyperglycemia has the strongest relation to increased incidence of congestive heart failure in patients with metabolic syndrome and MI. Given the ever-increasing prevalence of metabolic syndrome worldwide, this finding has important clinical implications and confirms the importance of evaluating glycemic control during the acute phase of MI.