Presence of Metabolic Syndrome is not an Independent Predictor of In-hospital Adverse Events in Patients with ST Elevation Myocardial Infarction that Underwent Primary Percutaneous Coronary Intervention

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Abstract

Background: Presence of Metabolic Syndrome (MetS) has been shown to predict higher risk for cardiovascular diseases. However, in patients with ST Segment Elevation Myocardial Infarction (STEMI), prognostic importance of MetS has not been widely studied.

Methods: We prospectively recruited 611 STEMI patients (521 male, 90 female) who were treated by primary angioplasty. Metabolic syndrome was diagnosed according to the International Diabetes Federation metabolic syndrome worldwide definition. Coronary angiographic data and in-hospital events of individuals were recorded. Major Adverse Cardiac Events (MACE) included cardiac death, recurrent myocardial infarction and target lesion revascularization.

Results: Metabolic syndrome group included 276 (45.1% of the study cohort; mean age 56.8 ± 12.2; 210 male) and control group included 335 subjects (54.9% of the study cohort; mean age 55.6 ± 12.9; 311 male). The frequency of female gender, hypertension, Diabetes Mellitus (DM), hyperlipidemia and positive history for coronary artery disease were higher in MetS group, whereas, the ratio of smokers was higher in the control group. The incidence of in-hospital death and MACE was not statistically different in MetS and control groups. Presence of MetS was not correlated with in-hospital death and MACE in univariate analysis. In multivariate analysis using model adjusted for age, gender, DM/ fasting glucose >100 mg/dl, left ventricular ejection fraction, post-PCI TIMI flow grade <3 and high creatinine and peak CK-MB levels age, peak CK-MB and creatinine levels remained the independent predictors of in-hospital mortality. Peak CK-MB and creatinine levels were also independent predictors of in-hospital MACE.

Conclusion: Presence of MetS was not a predictor of in-hospital adverse events in patients with STEMI treated with primary percutaneous intervention. Peak CK-MB and creatinine levels may indicate higher risk for in-hospital adverse events.

Keywords: Metabolic syndrome; ST-elevation myocardial infarction; Mortality; Major adverse cardiac events

Introduction

Raised blood pressure, and not only hypertension (HT), is included in metabolic syndrome (MetS). Metabolic syndrome is a combination of medical disorders that, included HT, obesity, and a prediabetic state (high fasting blood glucose, high triglycerides, and low High Density Lipoproteins (HDL)) [1]. It is rapidly increasing in prevalence when occurring together, increase the risk of developing cardiovascular disease (CVD) [1]. MetS traits co-occur, patients identified with one or just a few traits are likely to have other traits, as well as insulin resistance. Insulin resistance, associated hyperinsulinemia and hyperglycemia, and adipocyte cytokines may also lead to vascular endothelial dysfunction, abnormal lipid profile, HT, and vascular inflammation, all of which promote the development of atherosclerotic CVD [2-4]. There are several definitions for the MetS, leading to some difficulty in comparing data from studies using different criteria. Most recently, in 2009, the International Diabetes Federation Task Force for epidemiology and prevention of metabolic syndrome definitions is the last one that is being used [5]. Some meta-analysis, which includes many of the same studies, found that the MetS increases the risk for incident CVD [6-8]. The increased risk appears to be related to the risk factor clustering or insulin resistance associated with the MetS rather than simply to obesity. This was illustrated by the following studies: In a study of the Framingham population, obese people without MetS did not have a significantly increased risk of diabetes or CVD. Obese people with the MetS had a 10-fold increased risk for diabetes and a two-fold increased risk for CVD relative to normal weight people without the MetS [9]. Solymoss also showed that increasing MetS score was significantly related to more severe coronary angiographic alterations and higher frequencies of unstable angina, myocardial infarction, Percutaneous Coronary Intervention (PCI), and Coronary Artery Bypass Grafting (CABG). Although there is a certain relation between cardiovascular events and MetS, after Acute Coronary Syndrome (ACS) especially ST elevation myocardial infarction (STEMI) treated with primary PCI, we don’t have enough data about Major Adverse Cardiac Events (MACE) in patients with MetS. The hypothesis we wish to test is that the presence of MetS is associated with poor outcomes after primary PCI of STEMI.
Methods

Patient population

We prospectively evaluated 611 consecutive patients with STEMI who were admitted to the emergency department of our hospital and underwent cardiac catheterization procedures between December 2009 and June 2010. Patients were enrolled in the study if they fulfilled the following criteria: (i) presenting within 12 h from the onset of symptom (typical chest pain lasting for >30 min); (ii) ST segment elevation of more than or equal to 2 mm in at least two contiguous electrocardiogram leads or new onset of complete left bundle-branch block; (iii) treatment with primary PCI (angioplasty and/or stent deployment). Exclusion criteria were: no indication for PCI, treated with coronary bypass surgery (i.e. not suitable for PCI), and missing or unavailable data. All primary PCI procedures were performed in a single high-volume tertiary center (>3000 PCI/year) by expert operators performing more than 75 PCIs per year. The study protocol was approved by the hospital’s Ethics Committee.

Data sources

Demographic information and the clinical history of risk factors such as age, sex, diabetes mellitus (DM), HT, hypercholesterolemia, smoking, family history for coronary artery disease (CAD), myocardial infarction history, PCI or bypass history, and earlier drug use were determined from patients and medical records. Angina-to-reperfusion time and door-to-balloon time, heart rate, blood pressure, and body mass index were calculated. Laboratory parameters were determined at hospital admission and on a daily basis during the hospital stay. Fasting blood samples obtained within 24 hours of admission were used for the definition of MetS. Transthoracic echocardiography was performed by using a system V (Vingmed, GE, Horten, Norway) with a 2.5-MHz phased-array transducer. Recordings were taken on patients positioned in the left lateral decubitus position. The left ventricular ejection fraction was measured using a modified Simpson’s rule [10].

Coronary angiography, primary angioplasty, and stenting

All patients received chewable aspirin (300 mg, unless contraindicated) and clopidogrel (300 mg, loading dose) before coronary angiography. Angiographic data of the patients were obtained from the cardiac catheterization laboratory records. Emergency coronary angiography was performed by the percutaneous femoral approach. In all cases, non-ionic low-osmolality contrast media was used. The contra lateral artery was first injected. Infarct-related artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification [11]. Heparin (10000 U) was administered after coronary anatomy was defined. Coronary artery stenosis of more than 50% was considered clinically significant. Occlusion of the infarct related artery was crossed by using a 0.014-inch guide wire. Primary coronary interventions including balloon angioplasty and/or stent implantation were performed only for infarct related artery according to lesion anatomy. For each procedure, interventional success at the acute phase was defined as an obstruction and stenosis of the infarct related artery having been reduced to less than 50% stenosis with TIMI 2 or 3 flows after primary PCI.

After angioplasty, all patients were admitted to the coronary care unit, where 500 U/h of intravenous heparin or 1 mg/kg/day of subcutaneous low-molecular weight heparin were given; aspirin (100 mg) and clopidogrel (75 mg) were continued in all patients. Tirofiban was used if angiographically evidence of massive thrombus, thrombotic complications or slow or no-reflow was seen.

Definition

Metabolic syndrome was diagnosed according to the International Diabetes Federation Task Force on epidemiology and prevention [5]. Those criteria require the presence of 3 or more of the following:

1. Abdominal obesity (waist circumference >94 cm in men and >80 cm in women);
2. A high triglyceride level ≥ 1.7 mmol/L (≥150 mg/dL);
3. A low high-density lipoprotein cholesterol level <1.0 mmol/L for men, and <1.3 mmol/L for women (<40 mg/dL for men and <50 mg/dL for women);
4. Anti-hypertensive treatment or history of HT; systolic >130 and/or diastolic ≥ 85 mmHg.
5. Elevated fasting blood glucose concentration ≥ 5.6 mmol/L (≥ 100 mg/dL) or treatment for elevated blood glucose.

HT was defined as a history of HT for more than 1 year, which required the initiation of antihypertensive therapy by the primary physician. As patients received antihypertensive therapy during hospitalization, blood pressure recordings the day of discharge have been used in analyses. DM and impaired fasting glucose level were defined according to revised American Diabetes Association definitions. Patients were classified as having diabetes if they had a history of diagnosed DM or if their mean fasting blood glucose level was at least 126 mg/dL. The lowest of the measurements during hospitalization period has been used for the analyses. Positive family history for CAD was defined as documented evidence of CAD in a parent or sibling before 60 years of age. The reperfusion time was defined as the time from symptom onset of chest pain to first balloon inflation. Patients were evaluated according to the Killip clinical examination classification [12]. Acute stent thrombosis is defined as an abrupt onset of cardiac symptoms (i.e. an ACS) along with an elevation in levels of biomarkers or electrocardiographic evidence of myocardial injury after stent deployment in the first 24 h, which is accompanied by angiographic evidence of a flow-limiting thrombus near a previously placed stent. Reinfection was described as an elevation of serum creatine kinase-MB enzyme levels by two times the upper limit of normal and ST segment re-elevations. MACE was defined as cardiovascular mortality, reinfarction, and repeat target vessel revascularization (percutaneous or surgical).

Statistical Analysis

Quantitative variables were expressed as mean value ± standard deviation, and qualitative variables were expressed as percentage (%). The characteristics of the groups were compared by the use of analysis of variance for continuous variables and by the chi [2]-statistic for categorical variables. Backward stepwise multivariate logistic regression analysis, which included variables with a p value of less than 0.1, was carried out to identify independent predictors of in-hospital mortality. Sex, age, DM, HT, post-PCI TIMI grade, left ventricular ejection fraction, peak CK-MB and creatinine levels were entered into the model. A p value of less than 0.05 was considered statistically significant. All statistical studies were carried out with the SPSS program (version 15.0, SPSS, Chicago, Illinois, USA).

Results

The demographic and clinical findings of study groups according to the presence or absence of MetS are depicted in table 1. In MetS group, the frequency of female gender, HT, DM, hyperlipidemia and
positive history for CAD were higher, whereas, in patients without MetS frequency of smokers was higher than MetS group. Waist circumference was significantly higher in MetS group (95.4 ± 1.2 vs. 88.3 ± 10.1 cm; p=0.01). In addition, plasma fasting triglycerides and glucose levels were significantly higher in MetS group whereas HDL cholesterol levels were higher in controls.

The incidence of death, recurrent MI and target vessel revascularization were not statistically different between MetS group and controls (Tables 2 and 3). In univariate regression analysis age, gender, DM/fasting glucose >100 mg/dL, left ventricular ejection fraction, post-PCI TIMI flow grade <3 and high creatinine and peak CK-MB levels were correlated with in-hospital death. However, in multivariate analysis only age, peak CK-MB and creatinine levels remained the independent predictors of in-hospital mortality. Peak CK-MB and creatinine levels were the only independent predictors of in hospital MACE. Presence of MetS or any of the MetS components were not independent predictors of in-hospital adverse cardiovascular events.

**Discussion**

In this prospective study we showed that presence of MetS according to NCEP-R is not an independent predictor of in-hospital mortality and MACE in patients with STEMI who is undergoing primary PCI. Patients with DM or hyperglycemia have higher risk for in-hospital MACE even if they do not fulfill the other criteria for MetS.

The MetS is one of the major public health problems of this century. In a cohort of Turkish population, diagnosed by the NCEP ATP III criteria, the prevalence of MetS was very high with a reported rate of 33.9% [13]. We also found on admission the prevalence of MetS was 42.7% in patients hospitalized with STEMI, a finding which showed a higher prevalence of MetS in patients with STEMI, is consistent with

| Table 1: Baseline characteristics, laboratory findings and clinical outcomes in STEMI patients according to the presence of metabolic syndrome. |
|---------------------------------------------------------------|
| **Metabolic syndrome (n=276)** | **Control (n=335)** | **p** |
| Age, years | 56.8 ± 12.2 | 55.6 ± 12.9 | 0.26 |
| Male, n (%) | 210 (76%) | 311 (92%) | 0.01 |
| Height, (m) | 1.69 ± 0.08 | 1.71 ± 0.06 | 0.07 |
| Weight, (kg) | 84.8 ± 13.9 | 77.2 ± 12.2 | 0.01 |
| BMI, kg/m² | 29.4 ± 4.5 | 26.2 ± 3.6 | 0.01 |
| Smoking, n (%) | 181 (66%) | 273 (81%) | 0.01 |
| Hypertension, n (%) | 87 (32%) | 55 (16%) | 0.01 |
| Prior myocardial infarction, n (%) | 100 (36%) | 91 (27%) | 0.02 |
| Systolic blood pressure, mmHg | 125 ± 25 | 123 ± 24 | 0.24 |
| Diastolic blood pressure, mmHg | 76 ± 15 | 74 ± 14 | 0.33 |
| Killip class >1, n (%) | 15 (5%) | 23 (7%) | 0.46 |
| Anterior myocardial infarction, n (%) | 130 (47%) | 165 (49%) | 0.59 |
| Reperfusion time, min | 210 ± 130 | 215 ± 145 | 0.69 |
| Post PCI TIMI 3 flow, n (%) | 286 (98%) | 330 (99%) | 0.09 |
| Left ventricular EF, % | 45.1 ± 8.6 | 46.1 ± 8.2 | 0.13 |

**Components of metabolic syndrome**

- Diabetes mellitus or fasting glucose > 100 mg/dL, n (%) | 234 (85%) | 77 (23%) | 0.01 |
- Hypertension, n (%) | 184 (67%) | 63 (19%) | 0.01 |
- Waist circumference, cm | 95.4 ± 12.2 | 88.3 ± 10.1 | 0.01 |
- HDL cholesterol, mg/dL | 37.3 ± 9.9 | 40.9 ± 11.3 | 0.01 |
- Triglycerides, mg/dL | 181 (98%) | 111 (60%) | 0.01 |
- Fasting glucose level, mg/dL | 121 (47) | 101 (28) | 0.01 |

**Laboratory findings**

- Creatinine, mg/dL | 0.92 ± 0.37 | 0.87 ± 0.28 | 0.08 |
- Peak CK-MB, U/L | 128 (140) | 143 (181) | 0.12 |
- Hemoglobin, g/dL | 14.1 ± 2.4 | 14.2 ± 1.6 | 0.48 |
- Platelet, 10⁹ /µL | 254 ± 79 | 247 ± 72 | 0.22 |
- Total cholesterol, mg/dL | 184 (55) | 195 (57) | 0.11 |
- LDL cholesterol, mg/dL | 124.8 ± 37.3 | 117.9 ± 36.7 | 0.04 |

Parametric variables are reported in mean ± SD or median (inter-quartile range); categorical variables are reported in number (percentage); BMI: Body Mass Index, CAD: Coronary Artery Disease, Post-PCI: Post-primary Coronary Intervention, EF: Ejection Fraction, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein

| Table 2: Comparison of incidence of in-hospital adverse events in metabolic syndrome patients and controls. |
|---------------------------------------------------------------|
| **MetS (n=276)** | **Control (n=335)** | **p** |
| In-hospital clinical outcomes n (%) | | | |
| Acute stent thrombosis, n (%) | 5 (2%) | 9 (3%) | 0.47 |
| Recurrent myocardial infarction, n (%) | 7 (3%) | 9 (3%) | 0.90 |
| Target lesion revascularization, n (%) | 6 (2%) | 9 (3%) | 0.69 |
| Death, n (%) | 11 (4%) | 7 (2%) | 0.17 |
| Major adverse cardiac events, n (%) | 18 (7%) | 17 (5%) | 0.44 |

Death, recurrent myocardial infarction and target lesion revascularization are accepted as major adverse cardiac events.
showed that MetS was associated with increased risk of in-hospital mortality, but did not show the meaningful increment of poor long term clinical outcomes [25]. In some studies of Japan and Turkish patients, there was no association between MetS and cardiac death, whereas the risk of combined cardiac events of cardiac death and nonfatal MI was significantly increased in patients with MetS [15,26]. And an interesting finding from a prospective follow-up study of French patients with ACS was that, although total mortality in patients with MetS compared to those without have increased, minor and major cardiovascular events did not differ [27].

Reasons of these conflict finding are, MetS may be re-defined for each ethnic groups, thus our data are similarly in same ethnic group [14]. The percentage of the women in our study might have contributed to the negative findings, because some of the previous studies have shown MetS and DM as stronger predictors for future cardiovascular events in women compared with men [28-30]. And early revascularization in experienced hands may be positive impact on MACE and mortality.

While MetS and its components have consistently been associated with ACS developed, MetS did not correlate with in-hospital mortality and MACE. An important result of our study was that hyperglycemia was the only component of MetS associated with increased risk of in-hospital events. Several hypotheses may explain the role of hyperglycaemia in the worse prognosis in ACS. Admission blood glucose is a common acute adrenergic signal of stress and is present in MI [31], as well as other severe acute illnesses [32] whereas increased

| In-hospital death | Univariate analysis | Multivariate analysis* |
|-------------------|---------------------|-----------------------|
|                   | OR (95% CI)         | p                     | OR (95% CI)         | p                     |
| Age, years        | 1.07 (1.03-1.12)    | 0.01                  | 1.05 (1.001-1.11)   | 0.05                  |
| Male gender       | 0.26 (0.11-0.67)    | 0.01                  | 0.26 (0.06-1.09)    | 0.06                  |
| Smoking           | 0.53 (0.21-1.39)    | 0.20                  |                       |                       |
| Reperfusion time, min | 1.00 (0.99-1.01) | 0.40                  |                       |                       |
| Left ventricular EF, % | 0.86 (0.82-0.91) | 0.01                  | 0.95 (0.89-1.01)    | 0.12                  |
| Post-PCI TIMI flow <3 | 9.71 (2.48-38.1) | 0.01                  | 3.32 (0.48-22.9)    | 0.22                  |
| Peak CK-MB (U/L)  | 1.005 (1.003-1.007) | 0.01                 | 1.006 (1.003-1.009) | 0.01                  |
| Creatinine levels (mg/dL) | 10.7 (4.6-24.5) | 0.01                  | 8.04 (2.9-22.2)     | 0.01                  |
| Hypertension / BP>130/85mmHg | 2.37 (0.90-6.21) | 0.08                  | 1.58 (0.39-6.49)    | 0.52                  |
| Central obesity; WC >94 cm for men, > 80 cm for women | 1.57 (0.61-4.1) | 0.35                  |                       |                       |
| DM / fasting glucose >100 mg/dL | 4.01 (0.91-17.6) | 0.07                  | 2.58 (0.40-9.55)    | 0.32                  |
| Triglycerides >150 mg/dL | 0.84 (0.31-2.20) | 0.73                  |                       |                       |
| HDL cholesterol; <40mg/dL for men, < 50mg/dL for women | 0.63 (0.23-1.65) | 0.37                  |                       |                       |
| Presence of metabolic syndrome | 1.95 (0.75-5.01) | 0.18                  |                       |                       |

| In-hospital MACE | Univariate analysis | Multivariate analysis* |
|-------------------|---------------------|-----------------------|
|                   | OR (95% CI)         | p                     | OR (95% CI)         | p                     |
| Age, years        | 1.04 (1.01-1.07)    | 0.01                  | 1.02 (0.99-1.05)    | 0.21                  |
| Male gender       | 0.55 (0.24-1.27)    | 0.16                  |                       |                       |
| Smoking           | 1.17 (0.52-2.64)    | 0.69                  |                       |                       |
| Reperfusion time, min | 1.00 (0.99-1.002) | 0.66                  |                       |                       |
| Left ventricular EF, % | 0.92 (0.88-0.96) | 0.01                  | 0.97 (0.93-1.02)    | 0.32                  |
| Post-PCI TIMI flow <3 | 4.14 (1.18-16.4) | 0.03                  | 2.04 (0.47-8.87)    | 0.34                  |
| Peak CK-MB , U/L  | 1.003 (1.002-1.005) | 0.01                 | 1.003 (1.001-1.005) | 0.01                  |
| Creatinine , mg/dL | 7.61 (3.63-15.9)   | 0.01                  | 4.80 (2.18-9.96)    | 0.01                  |
| Hypertension / TA>130/85mmHg | 1.79 (0.90-3.55) | 0.09                  | 1.36 (0.61-2.98)    | 0.45                  |
| Central obesity; >94 cm for men, > 80 cm for women | 0.90 (0.44-1.84) | 0.78                  |                       |                       |
| DM / fasting glucose >100 mg/dL | 3.11 (1.17-7.97) | 0.02                  | 2.16 (0.78-5.97)    | 0.14                  |
| Triglycerides >150 mg/dL | 0.58 (0.28-1.21) | 0.17                  |                       |                       |
| HDL cholesterol; <40mg/dL for men; < 50mg/dL for women | 1.07 (0.53-2.14) | 0.83                  |                       |                       |
| Presence of metabolic syndrome | 1.30 (0.65-2.57) | 0.45                  |                       |                       |

*Variables with p values <0.10 in univariate analyses were included in multivariate regression analysis. EF: Ejection Fraction, Post-PCI: Post-Primary Coronary Intervention, BP: Blood Pressure, WC: Waist Circumference, DM: Diabetes Mellitus, HDL: High Density Lipoprotein

Table 3: Univariate and multivariate analysis for the predictors of in-hospital death and major adverse cardiac events (MACE).
hyperglycemia is frequent. We could overdiagnose hyperglycemia as applicable to the whole acute myocardial infarction patients. Fasting acute myocardial infarction patients that underwent primary PCI. may not be generalized to other populations. We just evaluate the our data may be quite specific to Turkish population and therefore, selection bias. We did not evaluate long-term outcomes. However, 10.

Study Limitations

In this study, single-center data were used, which could result in selection bias. We did not evaluate long-term outcomes. However, our data may be quite specific to Turkish population and therefore, may not be generalized to other populations. We just evaluate the acute myocardial infarction patients that underwent primary PCI. Patients that were not eligible for primary PCI and underwent CABG were not included in the study. That is why study findings may not be applicable to the whole acute myocardial infarction patients. Fasting blood samples obtained within 24 hours of admission were used for the definition of MetS. At the acute phase of the acute myocardial infarction hyperglycemia is frequent. We could overdiagnose hyperglycemia as MetS and this could affect the results of the study.

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