

Management and In-Hospital Outcome of Patients with First Episode of Acute Myocardial Infarction: Impact of Diabetes Mellitus

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The aim of this study is to compare clinical characteristics, management, complications, in-hospital outcome and mortality of diabetic and nondiabetic patients after the first episode of acute myocardial infarction (MI). This retrospective case-matched study included 60 diabetic and 55 nondiabetic patients. Medical information about patients was retrieved from the hospital recordings. Diabetic patients were older, were more hypertensive and had more coronary artery disease history than nondiabetic patients. The frequency of use of acute reperfusion therapy modalities was not statistically different between the two groups. Diabetes was a significant determinant against the use of beta blockers (OR=0.26; 95% CI 0.06–0.95) but in favor of angiotensin converting enzyme inhibitors (OR=3.3; 95% CI 1.17–9.36), whereas diabetes did not influence the use of other drugs. Diabetic patients had more complications than nondiabetic patients (40.0% and 16.3%, respectively, $p=0.005$). In-hospital mortality rate for diabetic patients was comparable to nondiabetic patients (16.7% and 10.9%, respectively, $p=0.373$). Pharmaceutical treatment regimens, particularly beta blockers, are underutilized after acute MI in diabetic patients. More frequent use of these regimens will improve the high complication and mortality rates in diabetic patients as well as in nondiabetic patients.

Key words: diabetes mellitus ■ acute myocardial infarction ■ mortality ■ beta blockers ■ ACE inhibitors

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INTRODUCTION

D diabetes mellitus (DM) is an epidemic, and its prevalence was estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025.¹ Patients

with DM are at increased risk of developing cardiovascular diseases and have greater morbidity and mortality.² It has been shown that diabetic patients without previous myocardial infarction (MI) and cardiovascular disease have as high a risk of MI as nondiabetic patients with previous MI and cardiovascular disease.^{3,4} It has also been documented that in-hospital and long-term morbidity and mortality are increased in patients with diabetes.⁴⁻⁹ Despite a decline in heart disease mortality due to reduction in cardiovascular risk factors and improvement in the treatment of heart disease in the past 30 years, mortality for diabetic patients still remains high.^{10,11} Although current guidelines suggest aggressive management of MI¹²⁻¹⁴ and randomized clinical trials have proven the benefit of acute reperfusion therapy and targeted and long-term pharmaceutical treatment after MI,¹⁵⁻²⁰ these treatment regimens are still underutilized in diabetic patient population.^{5,21-25}

The aim of this study is to compare the baseline clinical characteristics, initial management, complications and in-hospital outcome of diabetic and nondiabetic patients after the first episode of MI who were hospitalized in the coronary care unit of our university hospital.

MATERIALS AND METHODS

This is a retrospective case-matched study in which medical information about consecutive patients with first episode of acute MI who admitted to Hacettepe University Hospital, Ankara, Turkey, and hospitalized in the coronary care unit within 24 hours after the onset of symptoms in the year 2003 was retrieved from the hospital recordings. Our hospital is a tertiary care hospital. Acute MI is diagnosed according to the updated American College of Cardiology (ACC)/European Society of Cardiology (ESC) definition, by either a typical rise and gradual fall of troponin levels and a more rapid rise and fall of creatine kinase MB levels—biochemical markers of myocardial necrosis—with ≥ 1 of the following: 1) ischemic symptoms, 2) development of pathologic Q wave on electrocardiography, 3) electrocardiographic changes indicative of myocardial ischemia (i.e., ST-seg-

ment elevation or depression), or 4) coronary artery intervention.²⁶ Reperfusion therapy modalities were chosen according to the 1999 update of ACC/American Heart Association (AHA) guidelines for the management of patients with acute MI.²⁷ The diagnosis of DM was based either on the information obtained from hospital recordings as chronic treatment with insulin or oral hypoglycemic agents or defined according to the criteria of American Diabetes Association.²⁸ All diabetic patients had type-2 DM. Among diabetic patients, 11 (18.3%) received insulin [mixture of neutral protamine Hagedorn (NPH) and regular insulin], 23 (38.3%) received oral hypoglycemic agents (sulfonylurea and/or metformin) and 26 (43.3%) received diet alone during their hospitalization in coronary care unit. None of the patients received intensified insulin regimen. History of taking antihypertensive pills or blood pressure measurement >130/85 mmHg was defined as hypertension. All investigations were done in accordance with the Declaration of Helsinki.

Data on baseline clinical characteristics, concomitant diseases [hypertension, dyslipidemia and previous history of coronary artery disease (CAD)], initial management regarding the reperfusion therapy [thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG)], pharmacological treatment [beta blockers, angiotensin converting enzyme (ACE) inhibitors, statins, acetylsalicylic acid (ASA), clopidogrel, calcium channel blockers and nitrates], complications of MI and in-hospital outcome of diabetic and nondiabetic patients after the first episode of MI were recorded. Arrhythmias, pulmonary edema, cardiogenic shock, ketoacidosis,

congestive heart failure, stroke and next MI were regarded as complications of acute MI. Atrial fibrillation, ventricular tachycardia/fibrillation and bradyarrhythmias are all included in arrhythmias. Routine fasting plasma glucose, total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels measured in our laboratory were also recorded. Seventy-one (61.7%) patients presented with ST-segment elevation MI and 44 (38.3%) patients presented with non-Q-wave MI. Patients without complications of acute MI were hospitalized 2–3 days in the coronary care unit and 7–10 days thereafter in an intermediary unit. Patients with complications were followed longer.

Absolute numbers, percentages and means were used to describe the patient population. Percentages of thrombolytic therapy users, patients with pulmonary edema, cardiogenic shock, ketoacidosis, congestive heart failure, stroke and next MI were compared by Fisher's exact test since the expected frequencies were <5. In-hospital mortality rates and percentages of beta blocker use among patients who received insulin and who did not receive insulin were also compared by Fisher's exact test. Other categorical variables and percentages are compared by Chi-squared test. Continuous variables were compared by Student's t test. Odds ratios and 95% confidence intervals were calculated by logistic regression analysis, which was used to adjust for factors influencing the use of chronic pharmacological treatment and in-hospital mortality. A p value <0.05 was considered statistically significant. The tests were performed using SPSS® for Windows®, release 11.0 (Chicago, IL). Since the distributions of ST-segment elevation and non-Q-wave MI were similar between diabetic and

Table 1. Clinical characteristics, cardiovascular risk factors and use of acute reperfusion therapy for patients after first episode of acute MI (data are mean ± SEM)

	Diabetic Patients (n=60)	Nondiabetic Patients (n=55)	p Value
Mean age (years)	67.4 ± 1.5	60.4 ± 1.7	0.003
Male/female	44/16	37/18	NS
Fasting plasma glucose (mg/dl)	251.0 ± 17.6	112.6 ± 4.7	0.0001
Total cholesterol (mg/dl)	190.2 ± 7.7	242.7 ± 41.2	NS
LDL cholesterol (mg/dl)	114.9 ± 6.8	126.4 ± 6.3	NS
HDL cholesterol (mg/dl)	46.8 ± 2.1	44.8 ± 1.6	NS
Triglycerides (mg/dl)	149.5 ± 18.0	148.4 ± 15.1	NS
Anterior MI (%)	30.0	20.0	NS
Hypertension (%)	60.0	32.7	0.003
CAD history (%)	43.3	23.6	0.026
Dyslipidemia (%)	31.7	30.9	NS
Smoking (%)	51.7	65.5	NS
Family history of CAD (%)	23.3	16.4	NS
Thrombolytic therapy (%)*	86.5	91.2	NS**
PTCA (%)	16.7	12.7	NS
CABG (%)	20.0	18.2	NS

CABG: coronary artery bypass grafting; CAD: coronary artery disease; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; NS: not significant; PTCA: percutaneous transluminal coronary angioplasty; * Among patients with ST-segment elevation myocardial infarction only; ** Calculated by Fisher's exact test

nondiabetic patients (61.7% of diabetic patients and 61.8% of nondiabetic patients had ST-segment elevation MI, and 38.3% of diabetic patients and 38.2% of nondiabetic patients had non-Q-wave MI; p values >0.05), analysis was done by combining ST-segment elevation and non-Q-wave MI.

RESULTS

Detailed data of 115 patients with first episode of acute MI who were hospitalized in the coronary care unit in the year 2003 were available. There were 60 (52.2%) diabetic and 55 (47.8%) nondiabetic patients. Diabetic patients were older and had higher fasting plasma glucose levels than nondiabetic patients (Table 1). During hospitalization, mean fasting plasma glucose decreased significantly in diabetic patients (from 251 mg/dl to 149.6 mg/dl, p=0.003) but not in nondiabetic patients (from 112.6 mg/dl to 91.7 mg/dl, p=0.136). Mean fasting plasma glucose during follow-up did not differ between patients taking insulin and oral hypoglycemic agents (145.2 mg/dl vs. 139.6 mg/dl, p=0.634).

There were no statistically significant differences with regard to gender, lipid parameters and localization of MI. Regarding the risk factors and concomitant diseases, diabetic patients had more hypertension (60% vs. 32.7%, p=0.003) and CAD history (43.3% vs. 23.6%, p=0.026) than nondiabetic patients (Table 1). Frequencies of dyslipidemia, smoking and family history of CAD were not statistically different between the two groups. There were no statistically significant differences regarding the percentages of use of thrombolytic therapy (among patients

with ST-segment elevation MI only), PTCA and CABG between the two groups (Table 1).

Diabetic patients had more complications than nondiabetic patients (40.0% and 16.3%, respectively; p=0.005) (Table 2). However, the only statistically significant difference was achieved for arrhythmias (18.3% for diabetic patients and 3.6% for nondiabetic patients, p=0.013).

Diabetic patients received less beta blockers (38.3% vs. 69.1%, p=0.001) and clopidogrel (46.7% vs. 69.1%, p=0.015) than nondiabetic patients after acute MI. The use of statins, ACE inhibitors, calcium channel blockers, nitrates and ASA after acute MI did not differ between the two groups (Table 3). In a logistic regression analysis correcting for differences in age, gender, concomitant diseases and complications of acute MI, diabetes was a significant determinant against the use of beta blockers (OR=0.26; 95% CI 0.06–0.95) but in favor of ACE inhibitors (OR=3.3; 95% CI 1.17–9.36), whereas diabetes did not influence the use of clopidogrel (OR=0.88; 95% CI 0.32–2.42), statins (OR=1.21; 95% CI 0.39–3.71), calcium channel blockers (OR=0.76; 95% CI 0.20–2.77), nitrates (OR=0.86, 95% CI 0.31–2.44) and ASA (OR=0.72; 95% CI 0.14–3.64). In patients with diabetes, only age was found to be a predictor of avoidance of beta blockers. Patients who received beta blockers were younger than the patients who did not receive beta blockers (62.6 years vs. 70.3 years, p=0.01). Gender, presence of concomitant diseases and complications of acute MI did not predict the use or avoidance of beta blockers (data not shown).

Table 2. In-hospital complications after acute myocardial infarction

	Diabetic Patients (n=60)	Nondiabetic Patients (n=55)	p Value
Arrhythmias (%)	18.3	3.6	0.013*
Pulmonary edema (%)	5.0	3.6	NS**
Cardiogenic shock (%)	3.3	0	NS**
Ketoacidosis (%)	3.3	0	NS**
Congestive heart failure (%)	1.7	0	NS**
Stroke (%)	1.7	0	NS**
Next MI (%)	6.7	9.1	NS**
Total (%)	40.0	16.3	0.005*

MI: myocardial infarction; NS: not significant; * Calculated by Chi-squared test; ** Calculated by Fisher's exact test

Table 3. Pharmaceutical treatment regimens after acute myocardial infarction

	Diabetic Patients (n=60)	Nondiabetic Patients (n=55)	p Value
Beta blockers (%)	38.3	69.1	0.001
ACE inhibitors (%)	63.3	47.3	NS
Statins (%)	36.7	52.7	NS
ASA (%)	83.3	90.9	NS
Clopidogrel (%)	46.7	69.1	0.015
Calcium channel blockers (%)	20.0	16.4	NS
Nitrates (%)	61.7	54.5	NS

ACE: angiotensin converting enzyme; ASA: acetylsalicylic acid; MI: myocardial infarction; NS: not significant

Patients who received insulin were comparable to patients who did not receive insulin with regard to beta blocker use (45.5% vs. 36.7%, $p=0.734$).

In-hospital mortality was 16.7% for diabetic patients and 10.9% for nondiabetic patients, and this difference was not statistically significant ($p=0.373$). However, in a logistic regression analysis correcting for differences in age, gender, concomitant diseases, complications of acute MI, acute reperfusion therapy and chronic pharmaceutical treatment, DM was found to be a significant determinant of mortality (OR=2.40; 95% CI 1.55–2.98). There was no difference in in-hospital mortality rates between patients who received insulin and who did not receive insulin (9.1% vs. 18.4%, $p=0.671$).

DISCUSSION

Patients with DM have a 2–4-fold increased risk of developing CAD and have a greater morbidity and mortality.^{2,3} As diabetic patients without a previous history of MI and CAD have as high a risk of having MI as nondiabetic patients with a previous history of MI and CAD,^{3,4} DM should be considered and treated as a CAD equivalent. In this study, our aim was to compare diabetic and nondiabetic patients who were hospitalized in our coronary care unit with their first episode of MI with regard to utilization of current treatment protocols and in-hospital outcomes.

Diabetic patients were about seven years older, and had more hypertension and CAD history than nondiabetic patients. However, there was no gender difference, and frequencies of dyslipidemia, smoking and family history of CAD were not statistically different between the two groups. These findings are similar to the results of Gitt et al. and Norhammar et al.^{5,29}

There were no statistically significant differences between the two groups regarding the acute reperfusion therapy. However, approximately 17% of diabetic patients and 13% of nondiabetic patients were submitted to PTCA (Table 1). In the United States, >50% of patients with acute MI are submitted to PTCA. This difference might be due to the fact that low-budget medicine is utilized much more in our country compared to the high-budget medicine utilized in developed countries such as the United States. Even though 1999 practice guidelines of ACC/AHA were supposed to be followed at the time of this study, underutilization of PTCA is a striking result of our study. Apart from low-budget medicine stated above, physician preferences against the use of high-cost therapies may play a role in underutilization of PTCA.

Pharmaceutical treatment regimens were much more underutilized in diabetic patients than in nondiabetic patients. Diabetic patients received beta blockers, clopidogrel, ASA and statins less frequently than nondiabetic patients. However, statistically significant differences were only achieved for beta blockers and clopidogrel.

After adjustment for confounding factors, only beta blockers were found to be underutilized by diabetic patients and ACE inhibitors were found to be much more utilized. This finding is in accordance with the previous findings of Gitt et al.⁵ In our study, 38.3% of diabetic patients and 69.1% of nondiabetic patients received beta blockers. In the previous study by Gitt et al., beta blockers were significantly underutilized in diabetic patients compared to nondiabetic patients (66.2% and 70.7%, respectively; $p<0.001$). In a recent study by Hanania et al.,³⁰ the percentage of patients receiving beta blockers after acute MI was 71%. In the OASIS study,⁴ 59% of diabetic patients and 65% of nondiabetic patients after unstable angina or non-Q-wave MI were receiving beta blockers. These results demonstrate that our diabetic patients received beta blockers less frequently than the diabetic patients reported previously. However, the percentage of nondiabetic patients who received beta blockers in our study was similar to the percentages in other studies. Since beta blockers were proven to be protective against next MI and early and long-term mortality, underutilization of beta blockers may explain the high in-hospital mortality rate for both diabetic and nondiabetic patients. Most clinicians avoid prescribing beta blockers in diabetic patients because of their adverse effects on glucose metabolism. In a recent population-based, retrospective cohort study by McDonald et al., the mortality of diabetic patients who received beta blockers was lower than that of the diabetic patients who did not receive beta blockers.³¹ After adjusting for clinical confounders and use of drugs with proven cardiovascular benefits, this significance was lost. Recurrent MI and 30-day rehospitalization rates also did not differ between groups. They concluded that benefits of beta blockers in diabetic patients might be much less than previously reported despite their similar adverse event rates as reflected by comparable rehospitalization rates with the control group. However, a large body of evidence from observational and large, randomized clinical trials and systematic reviews have shown that beta blockers are highly effective in reducing cardiovascular end points and overall mortality. In the U.K. Prospective Diabetes Study, it was demonstrated that beta blockers are at least as effective as ACE inhibitors in reducing macrovascular and microvascular complications.^{32,33} Therefore, beta blockers should be one of the first-line therapeutic regimens for all diabetic patients with established CAD or MI. In our opinion, the results of McDonald et al. should not change current clinical practice until more data become available.

After adjustment for confounding factors, diabetes was a determinant for the use of ACE inhibitors; 63.3% of diabetic patients and 47.3% of nondiabetic patients received ACE inhibitors. This finding is also in accordance with the previous studies that ACE inhibitors were much more utilized in diabetic patients than in

nondiabetic patients.^{4,5} In the OASIS registry, 36% of diabetic patients and 23% of nondiabetic patients received ACE inhibitors, much less than the frequencies found in our study.⁴ In the study of Gitt et al., 84.0% of diabetic patients and 73.5% of nondiabetic patients received ACE inhibitors.⁵ It is interesting to note that none of our patients received angiotensin-II receptor blockers at that time. We think that the high cost of angiotensin-II receptors blockers made the physicians avoid prescribing them and prefer ACE inhibitors. Although frequencies of utilization of other pharmaceutical regimens were similar between diabetic and nondiabetic patients, these regimens were still underutilized in nondiabetic patients as well as in diabetic patients.

Diabetic patients had more complications after acute MI than nondiabetic patients. Particularly arrhythmias were more common among diabetic patients (18.3% and 3.6%, respectively). Although no events of cardiogenic shock, ketoacidosis, congestive heart failure and stroke were reported among nondiabetic patients, the frequencies of these complications were not statistically different between diabetic and nondiabetic patients. This may be due to the small sample size of our patient population and the small number of patients with these complications even among diabetic patients, and the results achieved may easily reflect type-2 error.

This study demonstrated that the in-hospital mortality rate of diabetic patients after the first episode of acute MI was comparable to their nondiabetic counterparts. Although adjustments were done for confounding factors and DM was found to be an independent determinant for in-hospital mortality after the first episode of acute MI, the in-hospital mortality of the entire cohort with or without DM was still high when the total number of patients was considered. As stated previously, this may be due to the use of low-budget medicine reflected as the low percentage of patients submitted to PTCA and underutilization of chronic pharmaceutical treatment regimens or due to the referral of high-risk patients to a tertiary care center. Patients in both groups have higher rates of smoking than the patients in developed countries such as the United States. This may also be a factor in high mortality rates in both groups. Although intensified insulin therapy has proven to be beneficial after acute MI, none of our patients received intensified insulin regimen. The number of patients receiving NPH and regular insulin was also small. This may be another reason for the high in-hospital mortality rate in both patients with and without DM.

Although there has been a decline in mortality from heart disease in the past 30 years, preventive measures and improvement in treatment modalities should be undertaken in diabetic patients as well as in nondiabetic patients since the prevalence of DM is estimated to increase and will become a global burden.

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The University of Pennsylvania School of Medicine and The Philadelphia Veterans Administration Medical Center

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