Original Article

Impact of Diabetes on dynamics of serum myocardium biomarkers, infarct size, and In-hospital outcomes in patients with a First Acute Myocardial Infarction

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ABSTRACT

Objective: Diabetic patients with acute myocardial infarction (AMI) have poor prognosis. The aim of this study was to compare the influence of diabetes on prognosis after AMI by serial changes of serum myocardium biomarkers and infarct size.

Methodology: CK-MBmass and CK-MBact were measured by the microparticle enzyme immunoassay and immunoinhibition assay respectively. The size of the myocardial infarction area was calculated on the basis of serial changes.

Results: In diabetic AMI patients (n=72), the peak values of CK-MBmass and CK-MBact appeared at 23.1 h and 24.2 h, and maintained at peak level for 16.6 h and 17.3 h before returned to normal by 62.3 h and 69.2 h respectively. In contrary, the peak values of these enzymes in non-diabetic AMI surfers (n=154) returned to normal by 58.4 h and 63.2 h respectively (both P<0.01). Patients with diabetes also had larger infarct size as calculated by the serial serum measurements of CK-MBmass (47.3±10.5 vs 41.6±10.7, P<0.01) and CK-MBact (52.4±12.8 vs 46.9±13.4, P<0.01), accompanying with higher occurrences of arrhythmias (40.3% vs 29.9%, P<0.01), cardiac dysfunction (34.7% vs 24.0%, P<0.01), and mortality (11.1% vs 7.1%, P<0.01).

Conclusions: Diabetic patients with AMI are associated with increased release of serum myocardium biomarkers, larger infarct size, and higher incidence of in-hospital complications and mortality. These associations could explain the poor prognosis in diabetic patients with AMI.

KEY WORDS: Diabetes; Acute myocardial infarction; Dynamic changes; Infarct size; Prognosis.

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INTRODUCTION

Diabetes is regarded as a "cardiovascular disease risk equivalent".[1] A number of epidemiological studies have reported that patients with diabetes are more likely to experience myocardial infarction (MI) and have worse outcomes compared with non-diabetic individuals.[2,3]

Acute myocardial infarction (AMI) usually accompanies with the release of myocardium biomarkers into blood, which can be easily detected. In clinical practice, the frequently used serum myocardium biomarkers include myoglobin, creatine kinase-MBmass (CK-MBmass), creatine kinase-MBactivity (CK-MBact), cardiac troponin I (cTnI)

and cardiac troponin T (cTnT), which is either measured alone or in combination.[4] In addition to being a standard for diagnosis, serum myocardium biomarkers, especially with serial changes, have been shown to have additional clinical implications in predicting the severity of myocardial injuries after the AMI. For example, we recently reported that CK-MBmass could be used as an indicator of related artery reperfusion after thrombolysis and the kinetic changes of serum CK-MBmass could be used for the assessment of the status of related artery reperfusion in AMI.[5] Furthermore, previous studies have shown that assessment of these serial changes of serum myocardium biomarkers provided an accurate index of the extent of myocardial infarction,[6] which was recognized as the most important predictor of survival.[7]

In the current study, we aimed to determine the influence of diabetes on prognosis after AMI by examining the kinetic changes of serum myocardium biomarkers (CK-MBmass and CK-MBact) and infarct size. We hypothesize that diabetic patients would have higher levels of CK-MBmass and CK-MBact, larger infarct size and worse short-term outcomes.

METHODOLOGY

Study Population: From June 2002 to December 2007, a total of 226 patients with a first AMI and not eligible for thrombolytic treatment or emergency percutaneous coronary intervention (AMI without ST-segment elevation, history of chest pain lasting > 12 h, and other contraindications for above treatments) were enrolled in this study. AMI was defined by a combination of two of three characteristics: typical symptoms (that is, chest discomfort), increase in myocardium enzymes, and inverted Q waves in the electrocardiogram (ECG).[8] First AMI was defined by: (1) No previous history of AMI recorded; (2) First appearance of Q-waves on ECG recording. The enrolled patients were all treated with standard of care, including aspirin, β-blockers, nitrates, angiotensin-converting enzyme inhibitors, low molecular weight heparin and clopidogrel. The diabetes group was defined as patients with a known diagnosis of diabetes. The remaining patients were included in the control group.

The study conforms to the principles of the Declaration of Helsinki[9] and was approved by the Ethics Committee of the Qianfoshan Hospital. Signed consents were obtained from all patients who participated in this study.

ECG Analysis: To assess the serial ST-segment analysis and development of new Q waves, a 12-lead ECG recording was done on arrival, and every 2 hours up to 8 hours afterwards the treatment. ECGs were interpreted by 2 cardiologists who were specialized in doing and analyzing ECGs and did not know any details of our study (including unaware of DM status). The maximal ST-segment elevation (Max STE), ST resolution (STR), sum of ST-segment elevations (∑ST), and total area under the Q waves (∑Q) were measured as described previously.[10]

Biochemical assays: Blood samples (2ml) were immediately obtained just on the hospital presentation, and then every 4-8 hours, or at any time with any variation in state of the illness until CK-MBmass, CK-MBact and cTnI returned to normal. Levels of CK-MBmass and cTnI were measured by the microparticle enzyme immunoassay method using AXSYM kit (Abbott Company, USA). The normal range for CK-MBmass was 0-49.4 ng/ml and for cTnI was 0-0.04 ng/ml. Serum CK-MBact was measured using an immunoinhibition assay (Roch Company, Basle, Switzerland), with the normal range 0.2-24 IU/L.

Determination of infarct size: AMI size was calculated on the basis of serial changes of serum myocardium biomarkers as previously reported.[6] Briefly, cumulative release of CK-MBmass and CK-MBact, from the onset of AMI (t = 0) up to the serum level down to normal (t = T), is indicated by CK-MBr which was calculated by the following formula:

$$\text{CK-MBr} = \int_0^T f(t)dt = E(T) + kd\int_0^T E(t)dt$$

The parameters f(t) and kd represent the fractional rate constants for myocardium biomarkers release into the serum and elimination from plasma respectively. Subsequently, total myocardial infarct size (MIS) was calculated as following:

$$\text{MIS} = \text{CK-MBr} \times \text{body weight (Kg)} \times \text{K (constant value)}$$

Table-I: Clinical characteristics of both groups.

	Diabetes	*Non-diabetes*
Number of cases	72	154
Male (%)	41(56.9)	80(51.9)
Female (%)	31(43.1)	74(48.1)
Age (years)	58.24±8.31	62.45±10.25
Hospitalized time (days)	51.63±9.33	48.72±8.85

No differences were seen in sex ratio, age ranges and hospitalized time between the two groups.

Table-II: ECG analysis in diabetic versus non-diabetic patients.

	Diabetes (n=72)	*Non-diabetes (n=154)*	*t values*	*P values*
Max STE (mm)	3.29±0.53	3.15±0.49	1.9499	>0.05
∑ST (mm)	9.45±2.13	7.28±1.16	9.9087	<0.01
STR (%)	2.89±6.5	39.2±11.3	7.1927	<0.01
∑Q (mm2)	11.24±2.31	8.45±1.25	9.4608	<0.01

Max STE = maximal ST-segment elevation, STR = ST resolution, ∑ST = sum of ST-segment elevations, ∑Q = total area under the Q waves.

CK-MBmass-g and CK-MBact-g were used to represent the final calculated MIS which were based on the serial changes of CK-MBmass and CK-MBact respectively.

Coronary angiograph analysis: To judge the status of infarct-related arteries (IRA) and collateral circulation, coronary angiography was performed in all 226 cases of AMI after two weeks of treatment. All coronary angiograms were reviewed by three angiographers without knowledge of the clinical variables. The perfusion status of the IRA was determined in accordance with the Thrombolysis In Myocardial Infarction (TIMI) study classification.[11] Reperfusion was defined as TIMI flow grade 3, while no-reflow was defined as TIMI flow grade 0 or 1. The extent of collateral circulation was assessed in accordance with the method described before,[12] and the present of collateral circulation was considered if the grade ≥ 2.

In-hospital complications and mortality analysis: All enrolled patients, before their discharge from the hospital, information on the occurrence of arrhythmias, cardiac dysfunction, and death from all causes was obtained. Arrhythmias and cardiac dysfunction were defined as ≥ Lown grade 3 and ≥ Killip class II respectively. The cause of death included cardiac death, non-cardiac death or uncertain cause.

Statistical Analysis: Statistical analysis was performed with SPSS 12.0. Quantitative variables are presented as mean ± SD. Student *t* test was used to analyze continuous normally distributed variables. Differences between proportions were assessed by x^2 analysis. A 2-tailed $P<0.05$ was considered statistically significant.

RESULTS

Patient Population: During a period of 66 months, 226 patients (male: 157, female: 69) were enrolled in this study. The ages of the subjects ranged from 37 to 76 (61.4 ± 9.5). Among these patients, 72 (31.9%) had a history of diabetes. No differences were seen in sex ratio, age ranges and hospitalized time between the two groups (Table-I).

ECG and coronary angiograph analysis in diabetic versus non-diabetic patients: To assess the serial changes of ST-segment and Q waves, 12-lead ECGs were done and analyzed as described in the Methods. As shown in Table-II, except for the Max STE, values of ∑ST, STR, and ∑Q were all significantly higher in diabetic patients compared with those in non-diabetic patients (P<0.01).

All enrolled patients were confirmed for their disease status by coronary angiography, and angiogram characteristics were analyzed. Compared with the non-diabetic patients, diabetic patients suffered from more serious IRA perfusion status and worse collateral circulation (Table-III).

Kinetic changes of serum myocardium biomarkers: To determine impact of diabetes on the dynamic changes of myocardium biomarkers, we investigated the kinetics of serum CK-MBmass and CK-MBact in both groups. As shown in Table-IV, the abnormal values of CK-MBmass and CK-MBact appeared at 2.1 h and 2.3 h in diabetic patients, which were both 0.3 h later than in non-diabetic patients (P<0.01). The elevation rates of CK-MBmass and CK-MBact, from baseline up to the peak, were significantly prolonged in diabetic patients than in non-diabetic patients (P<0.01). Similar differences were also found for both the peak elevations and time up to

Table-III: Coronary angiography analysis in diabetic versus non-diabetic patients (%).

	n	*Reperfusion TIMI flow grade*			*Collateral circulation*
		3	2	0 or 1	
Diabetes	72	3 (4.2)*	6 (8.3)*	63 (87.5)*	4 (5.6)*
Non-diabetes	154	11 (7.1)	31 (20.1)	112 (72.7)	23 (14.9)

*P<0.05 compared with non-diabetic patients.

Table-IV: Serial changes of serum myocardium biomarkers.

	Diabetes (n=72)		*Non-diabetes (n=154)*	
	CK-MBmass	*CK-MBact*	*CK-MBmass*	*CK-MBact*
Abnormal appear (h)	2.1±0.4#	2.3±0.6#	1.8±0.5	2.0±0.6
Up to peak (h)	23.1±3.6#	24.2±3.8#	20.8±3.2	21.9±3.4
Elevation rates (h)	0.102±0.036#	0.091±0.032#	0.117±0.041	0.105±0.037
Peak elevations (ng/ml)	478.5±79.7#	268.4±63.6#	412.6±68.6	216.9±54.3
Peak duration (h)	16.6±3.8	17.3±3.7	15.6±3.5	16.4±3.5
Down to normal (h)	62.3±9.6#	69.2±11.0#	58.4±9.1	63.2±10.8
Resolution rates (h-1)	0.053±0.023#	0.046±0.021#	0.064±0.025	0.057±0.023

#P<0.01 compared with non-diabetic patients.

peak (P<0.01). The peak durations of CK-MBmass and CK-MBact were maintained for 16.6 h and 17.3 h before returning to baseline at 62.3 h and 69.2 h in diabetic patients. Compared with those in non-diabetic patients, no significant differences were seen in the peak durations, while diabetic patients had their peak values down to normal prolonged by 3.9 h and 6.0 h respectively (P<0.01). There were also significant differences for the resolution rates (from peak down to normal) of CK-MBmass and CK-MBact between two groups.

Comparison of infarct size and short-term outcomes in diabetic versus non-diabetic patients: To compare the influence of diabetes on the extent of myocardial damage and its relationship with the prognosis of AMI, we subsequently measured the infarct size in both groups as described in the Methods. Just in accordance with our anticipation, diabetic patients appeared to have larger infarct size as calculated by the serial changes of serum CK-MBmass (47.3±10.5 vs 41.6±10.7, P<0.01) and CK-MBact (52.4±12.8 vs 46.9±13.4, P<0.01). Similarly, when compared with the short-term outcomes, the occurrence of arrhythmias, cardiac dysfunction, and total mortality were all significantly higher in diabetic patients (Table-V).

DISCUSSION

This study shows that diabetic patients with AMI had increased release of serum myocardium biomarkers, larger infarct size, and higher risks of in-hospital complications and mortality. These results may explain, at least in part, the poor prognosis of diabetic patients with AMI compared with that of non-diabetic patients.

It is well established that patients with diabetes are at markedly increased risk of coronary artery disease (CAD). CAD develops earlier in the presence of diabetes and patients with diabetes have a risk of death from cardiovascular causes that is two to six times higher than in persons without diabetes.[13] Among CAD, AMI is regarded as the most serious one and may often be the first presentation in patients with diabetes.[14] In clinical practice, AMI is routinely accompanied with serial changes of serum myocardium biomarkers, and special appearances seen in ECG and coronary angiography. However, there is less clinical data on the impact of diabetes on the characteristics of above examinations.

As we all know, in spite of its own limitations, the 12 lead ECG stands at the center of risk stratification for the patient with suspected AMI. Previous studies have shown that persistent ST-segment elevation reflected sustained electrical transmural injury and correlated well with impaired myocardial reperfusion at the microcirculatory level.[15,16] In this study, our results showed that diabetic patients appeared to have higher sum of ST-segment elevations and prolonged ST resolution compared with those of non-diabetic patients (P<0.01), which suggested diabetic patients may suffer from worse impaired microvascular reperfusion.

To further determine the status of coronary flow, all enrolled patients were subsequently performed with coronary angiography, which is proposed as the gold standard for assessing reperfusion. As

Table-V: Relative risks of short-term outcomes after AMI (%).

	n	*Arrhythmias*	*Cardiac dysfunction*	*Total mortality*	*X2 values*	*P values*
Diabetes	72	29 (40.3)	25 (34.7)	8 (11.1)	15.3228	<0.01
Non-diabetes	154	46 (29.9)	37 (24.0)	11 (7.1)		

Arrhythmias and cardiac dysfunction were defined as ≥ Lown grade 3 and ≥ Killip class II respectively.
The cause of death included cardiac death, non-cardiac death or uncertain cause.

shown in Table-III, we determined up to 87.5% cases of diabetic patients with non-reperfusion, which are significantly higher than those in non-diabetic patients (72.7%, P<0.05). Meanwhile, when compared with control group, diabetic patients appeared to have lower proportion of continuous reperfusion (4.2% vs 7.1%, P<0.05) and collateral circulation (5.6% vs 14.9%, P<0.05). In agreement with previous reports,[17,18] our results confirmed that impaired microvascular flow and poor collateral recruitment were present in diabetic patients, which may be the possible explanations for increased cardiac adverse events in diabetic AMI patients. Several mechanisms are likely to contribute to the impaired microvascular circulation found in patients with diabetes, among which the focus is hyperglycemia induced endothelial injury and chronic vascular inflammation.[19] Just as one of our recent reports, activated nuclear factor-κB, a transcriptional complex and central regulator of inflammation, is overexpressed in aortas of CAD patients, especially in those with diabetes, and this expression correlates with the severity of coronary artery disease.[20] Therefore, high glucose concentration may be responsible for the worse endothelial injury and inflammation, which unavoidably result in the poor status of microvasculation found in patients with diabetes.

Besides ECG and coronary angiography, serum myocardium biomarkers are also useful indicators for AMI. In this study, we measured the dynamic changes of serum CK-MBmass and CK-MBact. Compared with non-diabetic patients, diabetic patients appeared to have higher peak values, and prolonged lasting time for both CK-MBmass and CK-MBact. These results indicate that diabetic patients may suffer from more serious myocardial necrosis, which were further proven by both the higher sum area under the pathological Q waves and larger infarct size found in diabetic patients. Furthermore, our results also showed that diabetic patients who had AMI appeared to have higher risks of cardiac complications, including death with all causes. These poor prognosis may be due to the larger infarct size found in diabetic patients, which is consistent with the previous report that larger infarct size is associated with increased mortality risk during short-term follow-up.[21]

Limitations of the Study: Several limitations should be noted. This is a single center study with a relatively small number of patients, thus possibly posing a risk of patient selection bias. In this study, the defined diabetic patients are those who had a known diagnosis. As we all know, results from the Euro Heart Survey[22] and the China Heart Survey[23] both indicated that abnormal glucose metabolism is common in patients admitted to hospital with CAD and is undiagnosed in the majority of them if only performed fasting plasma glucose level instead of oral glucose tolerance test (OGTT). However, due to the concern of acute glucose exposure or physical disability, especially for patients with a severe case like acute myocardial infarction, we did not routinely perform an OGTT for each patient in this research. So some diabetic patients may not have been diagnosed as having diabetes. In addition, due to the small sample size, we could not further discuss the differences of diabetic patients treated with insulin, oral hypoglycemic agents, or non-pharmacological treatment. To further reflect its clinical significance, future study should be extended to more centers. However, our data drawn from these samples indicate a consistent and significant tendency in diabetic patients.

In summary, our present study shows that diabetic AMI patients have higher levels of serum CK-MBmass and CK-MBact, larger infarct size, and worse short-term outcomes than non-diabetic AMI patients. Because of highly increased prevalence of diabetes who present with AMI, further studies should be performed on the implementation of therapies and strategies to lower morbidity and mortality in this vulnerable population.

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