Predicting clinical outcome in diabetics vs. non diabetics with Acute Myocardial Infarction after thrombolysis, using ECG as a tool

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Abstract

Objectives: To compare, the post Myocardial Infarction in-patient outcome after thrombolytic therapy in diabetics and non diabetics, in a South Asian population.

Methods: This was a prospective cross sectional study done at the Punjab Institute of Cardiology, Lahore from January to July 2009. Consecutive patients with ST elevation myocardial infarction, who were not treated with primary angioplasty but were thrombolysed were recruited at the time of arrival in the emergency department. Streptokinase was administered to all patients as the agent for thrombolysis. ECG was taken at baseline and at 60 minutes post streptokinase administration. Patients were subsequently divided into two groups: (A) Non Diabetics, (B) Diabetics.

This cohort was followed up through the in hospital stay for major complications which were recurrent ischaemic chest pain ,heart failure, arrhythmias and death.

Results: A total of 182 patients were included in the study, 146 males and 36 females. In non diabetic group, ST segment resolution occurred in 74 (84%) out of 88 patients and in diabetics, 13 (13.8%) out of 94 patients. In non diabetics, complications developed in 29 (32.9%) out of 88 patients and in diabetics, 75 (79.8%) out of 94 patients ($p< 0.001$). Diabetes with incorporate ST resolution compared to complete resolution were found to have more in hospital complications such as: recurrent chest pain (71.6% vs 23%, $p < 0.0001$), heart failure (39.5% vs 15.3%, $p= 0.0007$), arrhythmias (59.2% vs 15.3%, $p < 0.0001$), mortality (7.4% vs 0%, $p= 0.0082$). A similar trend was observed in non diabetics: recurrent chest pain (57.1% vs 17.5%, $p < 0.0001$), heart failure (42.8% vs 14.8%, $p= 0.0002$) and arrhythmias (50% vs 12.1%, $p < 0.0001$). Significant interaction was seen between diabetic status and ST segment resolution with respect to clinical outcome (recurrent chest pain $p < 0.0001$, heart failure $p = 0.025$, arrhythmias $p < 0.0001$, and death $p = 0.014$).

Conclusion: Diabetics with Acute Myocardial Infarction (AMI) encounter more adverse clinical outcome as predicted by incomplete ST resolution after thromboysis.

Keywords: Acute Myocardial Infarction (AMI), Thrombolysis, ST segment elevation (JPMA 61:1032; 2011).

Introduction

Acute Myocardial Infarction (AMI) can be considered as a potential epidemic for mankind (WHO, 1982). The incidence of coronary artery disease is rising in Pakistan. The acute coronary syndrome includes unstable angina, non-ST segment elevation MI (NSTEMI) and ST segment elevation MI (STEMI). Diabetes mellitus is one of the six primary risk factors identified for MI, others being dyslipidaemia, smoking, male gender, hypertension and family history of atherosclerotic arterial disease. Diabetes mellitus is a metabolic disorder which increases the rate of atherosclerosis progression of vascular occlusion.[1] Even after prompt thrombolysis the aftermath of diabetic patients is still worse than the non-diabetics, indicating impaired post thrombolysis left ventricular function and prognosis.

The aim of thrombolysis in acute MI is early and complete myocardial reperfusion.[2] Incomplete or failed reperfusion is associated with increased risk of complications. Analysis of ST-segment resolution on ECG, after fibrinolytic therapy, in cases of ST elevation Myocardial Infarction offers an attractive and cost effective solution to assess coronary reperfusion. Whereas coronary angiogram is a marker for epicardial reperfusion, ST segment resolution offers a better reflection of micro vascular reperfusion. Although successful thrombolysis of the epicardial vessel is necessary for good prognosis, but the micro-vascular flow more strongly correlates with the outcome. ST segment is therefore a better indicator of prognosis, and provides information, which cannot be assessed on basis of coronary angiogram alone.[3,4] In fact Schroeder et al[5] reported that absence of ST segment resolution was the most powerful independent predictor of early mortality ($p = 0.0001$). ST resolution can also be used as a tool to identify candidates for early invasive procedures such as PTCA, who are at risk of developing complications because of non resolution of ST segment after initial thrombolytic therapy.[6] Since ECG is widely available even in developing nations, it is important to establish its effectiveness as a tool for assessing reperfusion as it will offer the cheapest alternative for assessing recovery and myocardial salvage. The aim of our study was to correlate the incidence of complications with diabetes by using ST segment resolution as a tool, thereby re-enforcing the role of incomplete ST-resolution as a marker of worse clinical outcome in cases of diabetes with ST-elevated myocardial Infarction in our population.

Patients and Methods

The prospective study was conducted at Punjab Institute of Cardiology, from January 2009 to July 2009. All cases of acute Myocardial Infarction with the diagnosis based on WHO criteria i.e. presence of any two of the following were included.

1) Chest pain consistent with acute myocardial infarction of less than 24hrs duration, 2) Electrocardiography changes i.e. ST-segment elevation >0.2mv in at least two contiguous chest leads or >0.1mv in at least two contiguous limb leads, 3) New or presumably New left bundle branch block on Electrocardiogram and 4) raised levels of cardiac enzymes CPK-MB more than double of the reference value or positive Troponin I test done with commercially available kits of Trop I.

These patients came within 12 hours of chest pain and received Streptokinase on presentation.

Patients coming after 12 hours of chest pain and patients suffering from Type 1 diabetes mellitus were excluded.

The study population was divided into two groups:

GROUP-A; Non- Diabetics (n=88).

GROUP-B; Diabetics (n=94).

Only those patients who were known cases of diabetes or in whom it was established during hospital stay by repeated blood glucose estimation, were included in Group B.

A detailed history was taken, particularly of age, sex, occupation, address, history of smoking, Diabetes Mellitus, hypertension and family history of ischaemic heart disease. Complete physical examination of patients was done upon presentation in Emergency and important parameters such as pulse and blood pressure were noted. Patients were followed up daily. Pulse, ECG changes and complications if any were monitored till death or discharge of the patient. The end point was a composite of recurrent ischaemic chest pain, heart failure, arrhythmia or death.

Time from onset of chest pain to presentation of patient in emergency was noted through the history. ECG recordings of patients were taken upon presentation in Emergency. ST elevation was recorded in millimeters from the lead in which maximum elevation was observed. Injection Steptokinase was given intravenously to each patient at a dose of 1.5 million units, diluted in 100 ml of normal saline, in one hour.

Repeat ECG was performed after 60 minutes of administration of Streptokinase(SK). ST resolution was observed in the lead with the maximum ST elevation. ST resolution was defined as a reduction of $\geq 50\%$ ST segment elevation after thrombolysis. Informed written consent of the patient/attendant was taken. Follow up was conducted for each patient throughout his or her hospital stay. Fasting plasma glucose was recorded from all patients, in the morning of day following hospital admission. For differentiating new cases of diabetes, stress hyperglycaemia

and non-diabetic, fasting plasma glucose measurements were repeated in stable condition prior to discharge from hospital.

The patients were also assessed for the complications during the follow up. The major complications assessed were:

Recurrent ischaemic chest pain; Heart failure; Arrhythmia and Death.

Recurrent ischaemic chest pain was assessed on the basis of history and ECG, heart failure was assessed on the basis of clinical examination, chest X-ray, and echocardiography. Arrhythmia was evaluated on the basis of continuous bed side monitoring of ECG. Tachycardia was defined as pulse rate >100 and bradycardia as ≤ 50/minute.

Statistical analysis:

All data was analyzed by SPSS (statistical package for Social Sciences) version 12.0 for windows. Chi- Square test was used to compare the demographic characteristics and complication in both groups with 0.05% level of significance.

Results

A total of 182 patients were investigated in this study out of which 146 (80.2%) were males and 36 (29.8%) were females.

Table-1 shows the demographic characteristics of the study population at presentation. There was no significant difference in the co-morbidities of the two groups with hypertension showing the most significant trend. History of smoking and family history of atherosclerotic vascular disease was more common in group A while hypertension was more common in group B. Hypercholesterolemia was found to be almost equally prevalent in both groups.

Table-1: Demographic Data at time of presentation.

Demographic Characteristics	Non Diabetic (gp. A) n=88	Diabetic (gp. B) n=94
Mean Age (years)	53.34±13.38	56.30±11.26
Gender		
Male	74 (84.1%)	72 (76.6%)
Female	14 (15.9%)	22 (23.4%)
Time of thrombolysis in hours	5.68 ± 1.5	4.87 ± 2.3
Hypertension	30(34.1%)	46(48.9%)
Hypercholesterolemia	16(18.2%)	16(17.0%)
Family History	16(18.2%)	14(14.9%)
Smoking	48(54.5%)	42(44.7%)

Of the 182 consecutive patients investigated, 87 (47.8%) had complete ST segment resolution while 95 (52.2%) had failed ST segment resolution after 60 minutes of administration of streptokinase. Out of the 88 non diabetic patients, complete ST segment resolution was seen in 74 (84%) patients, while 14(16%) patients did not show ST segment resolution. Meanwhile out of 94 diabetic patients, only 13 (13.8%) showed complete ST segment resolution and 81(86%) patients had no resolution on their post-SK ECG. This was statistically significant P= < 0.001.

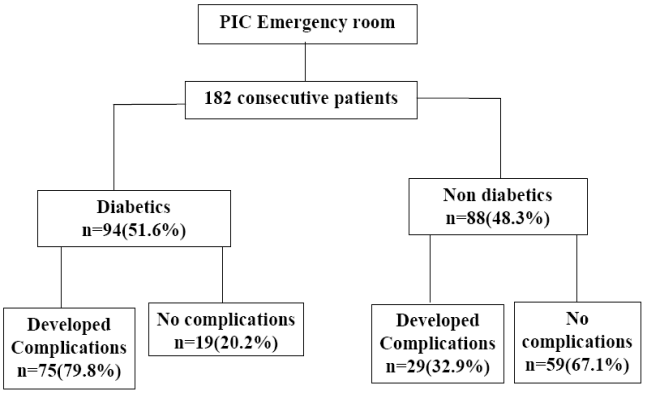

Figure: Frequency of complications between diabetics and non diabetics.

In group A, 29 (32.9%) patients developed complications during their follow up in the hospital. While in group B, 75 (79.8%) patients developed complications during their hospital stay (Figure).

The most common complications were recurrent ischaemic chest pain, Heart failure and arrhythmias. Table-2 shows the relationship of these complications with ST segment resolution between diabetics and non diabetics.

There was a statistically significant difference in the incidence of all the complications between the two groups as shown by the p-values in Table-2. Recurrent ischaemic chest pain was the commonest complication overall. In our study we noted that only 21(24%) patients from non diabetic group developed recurrent chest pain while 61(65%) patients from diabetic group developed recurrent chest pain in their early clinical outcome ($p < 0.0001$). ST segment resolution was associated with less frequency of occurrence of in-hospital recurrent ischaemia compared with incomplete resolution for both diabetics (23% vs. 71.6%, $p < 0.0001$) and nondiabetics (17.5% vs. 57.1%, $p < 0.0001$). The incidence of Heart failure was 19.3% in non diabetic patients and 36% in diabetic patients ($p = 0.025$), during follow up. ST segment resolution was associated with less frequency of occurrence of heart failure compared with incomplete resolution for both diabetics (15.3% vs. 39.5%, $p = 0.0007$) and nondiabetics (14.8% vs. 42.8%, $p = 0.0002$). We observed arrhythmias in 53% of the diabetic patients whereas 10% experienced arrhythmias in the non diabetic group.($p < 0.0001$). The results clearly show that arrhythmias are less frequent in non diabetic patients. ST segment resolution was associated with less frequency of occurrence of arrhythmias compared with incomplete resolution for both diabetics (15.3% vs. 59.2%, $p < 0.0001$) and nondiabetics (12.1% vs. 50%, $p < 0.0001$). Mortality in diabetic

Table-2: Relationship between ST segment resolution and In-hospital Events among diabetics and non diabetics.

	Non diabetic (total = 88)				Diabetic (total = 94)				* P value
	Composite (n = 88)	Complete ST resolution (n = 74)	Failed ST resolution (n = 14)	P value	Composite (n = 94)	Complete ST resolution (n = 13)	Failed ST resolution (n = 81)	P value	
Recurrent ischemic chest pain	21	13 (17.5%)	8 (57.1%)	<0.0001	61	3 (23%)	58 (71.6%)	<0.0001	<0.0001
Heart failure	17	11 (14.8%)	6 (42.8%)	0.0002	34	2 (15.3%)	32 (39.5%)	0.0007	0.025
Arrhythmia	16	9 (12.1%)	7 (50%)	<0.0001	50	2 (15.3%)	48 (59.2%)	<0.0001	<0.0001
Death	0	0	0	_	6	0	6 (7.4%)	0.0082	0.014

*Comparison of effect of diabetic status on ST segment changes (complete or failed resolution).

group was 6.4 % compared to 0% in non diabetic group. (p=0.014). ST segment resolution was associated with less frequency of deaths compared with incomplete resolution in diabetics (0% vs. 7.4%, p < 0.0082). Many diabetic patients in our study were observed to develop more than one complication.

Discussion

The time to reperfusion and complete reperfusion remain the key determinants for fibrinolysis. Historically ST resolution has been one of the markers used to assess reperfusion in STEMI. Its importance cannot be denied as a prognostic indicator and the results of our study also reinforce this fact. However its use as a cost effective marker has been underutilized. Several studies have reported similar angiographic[7,8] or ECG[9,10] success in both type 2 diabetic and non-diabetic subjects, while others have shown that the diabetics have less complete resolution of ST elevation than the non-diabetics.[11] To evaluate this issue, it has been hypothesized that type 2 diabetes might interfere with intravenous thrombolysis effectiveness, as estimated by angiographic or ECG criteria.

In our study we observed that in non-diabetic myocardial infarction 84% patients showed complete resolution and 16% showed failed resolution. But in case of diabetic myocardial infarction, 13.8% patients showed complete resolution and 86% showed failed resolution. In our study, more 'complete ST-resolution' was seen in non-diabetic patient (84% vs. 16%; p<0.001) whereas type 2 diabetic subjects were presented with significantly higher incidence of failed ST-resolution than non-diabetic subjects (86% vs. 13.8%; p<0.001). This significant change in ST-resolution between non-diabetic and diabetic group was similar with a study, which showed significant difference between diabetic and non-diabetic patients in relation to complete (34.1% vs. 68.2%; p<0.001) and incomplete (65.9% vs. 31.8%; p<0.001) resolution.[11] Our results are also consistent with a published meta-analysis in which it was shown that type 2 diabetic subjects had less ST resolution after intravenous thrombolysis administration compared with non-diabetic subjects.[7]

Our results showed the frequency of complications, in non diabetics to be 32.9% compared to 79.8% in diabetics (p<0.001), which was substantially higher in the latter. This finding therefore establishes a direct correlation between diabetes and the frequency of complications, as reflected by less complete ST segment resolution in diabetics in our study (86%)

In our study we noted that there was a significant interaction between diabetic status and failed ST resolution with respect to the occurrence of in-hospital recurrent ischaemia (p < 0.0001). Recurrent chest pain is the most common complication observed in this study. A study supporting our results showed that there was a significant interaction between diabetic status and treatment strategy with respect to the occurrence of in-hospital recurrent ischaemia.[12] In that study, 29.5% diabetics and 23.1% non diabetics developed recurrent ischaemia after fibrinolysis,(p < 0.001). As shown by another study, diabetic patients may have a greater residual lesion in the infarct related artery after treatment with fibrinolytics, resulting in a higher rate of recurrent ischaemia.[13]

In our results we observed that the interaction between diabetic status and failed ST resolution with respect to the development of heart failure was significant (p = 0.025). Heart failure is the major determinant for prognosis after myocardial infarction. Since some patients never had an echochardiography before this hospital admission to rule out prior heart failure, so any indication of heart failure post thrombolysis was considered as a new development. Our results are supported by the findings of a study which showed that in-hospital heart failure was more common among diabetics after fibrinolysis.[12] In that study, 9%diabetics and 4.3% non diabetics developed heart failure (p = 0.001).

We observed arrhythmias in 53% of the diabetic patients whereas 10% experienced arrhythmias in the non diabetic group (p < 0.0001). The results clearly show that arrhythmias are less frequent in non diabetic patients. Failed ST segment resolution was associated with high frequency of occurrence of arrhythmias compared with complete resolution for both diabetics (p < 0.0001) and nondiabetics (p < 0.0001). Our results are supported by a study in which incidence of AV block and LBBB, detected in half of the dying patients, was three times more common in diabetics

than in non-diabetic subjects.[14]

In our study mortality in diabetic group (only patients with failed ST resolution) was 6.4 % compared to 0% in non diabetic group.(P=0.014). A study supporting these findings was carried out by Timmer JR et al[15] According to their results, diabetes was associated with increased 30-day mortality. Diabetic mortality was 12.4% and non diabetic mortality 6.9% after thrombolysis at 30 day end point. Small sample size of this study limits our conclusions. there was no post hospital follow up, so that is another weak factor of this study. Since the hospital is equipped to deal with life threatening emergencies, in-hospital death as a complication was not that high in any group.

The negative influence of diabetes on outcome after STEMI has been described previously. Because mortality remains particularly high in patients with diabetes after STEMI, it is important to define optimal treatment strategies, including method of reperfusion therapy, in this population[16] In our study it was proved that reperfusion failed in a significant proportion of diabetic patients with STEMI in comparison with non-diabetic persons (86% vs. 16%). Similar results were obtained by Zairis et al.[11] They proved that Fibrinolysis may be less effective in diabetic patients. Angeja et al[7] showed that microvascular flow is decreased in diabetic patients after fibrinolysis. Possibly, this is associated with increased platelet aggregation and reduced ability to induce endothelium-mediated vasodilation.[17] The higher risk of adverse events may be caused by enhanced thrombogenicity and impaired fibrinolysis.[16] PCI can be a better alternative in diabetics presenting with acute MI. However, the long term outcome of these patients depends on the extent of coronary disease and residual left ventricular function, as well as the presence of other risk factors.[18] Hence, aggressive secondary preventive measures such as tight glycaemic control and lipid lowering may be just as important as the mode of reperfusion treatment for these patients. So, due attention is required for the better management of diabetic myocardial infarction patients. This should, however, be supplemented with further therapies and strategies directed towards the many abnormalities that are associated with diabetes, such as endothelial dysfunction, dysglycaemia and coagulation and fibrinolytic disturbances.

Our study was limited by the fact that the prognosis after ST elevation acute Myocardial Infarction is affected by various factors such as age, gender, number of coronary risk factors presented by the patient, use of aspirin with in 7 days, and number of angina attacks the patients' suffered.[19] We could not assess these factors, which correlate strongly with mortality in our study. A multi-variate analysis is required to exclude the importance of these confounding factors. Stress hyperglycaemia has a detrimental effect on thrombolytic outcome after acute myocardial infarction. Diabetes can be differentiated from stress hyperglycaemia with certainty only after the acute phase of the infarction. Thus, any attempt to identify undiagnosed diabetes in our study would have been biased because patients must survive the acute phase to be diagnosed. Another limiting factor was the non-randomized nature of the research and small size of patients included in the study. In addition to this it was also limited by the fact that it was a single centre study.

Conclusions

Frequency of in-hospital complications is more in failed ST resolution compared to complete ST resolution, in both diabetics and non diabetics, post thrombolysis. Diabetic population, after thrombolytic therapy, has a higher incidence of adverse clinical outcomes than non diabetics. Among diabetic patients with AMI, fibrinolysis was associated with less complete ST-segment resolution, suggesting impaired microvascular flow. Abnormal microvascular flow may contribute at least in part to the poorer outcomes observed in patients with diabetes and acute myocardial infarction.

References

1. Bajzer CT. Acute myocardial infarction. In: Medicine index. Cleveland Clinic Foundation, 2002; pp 222-6.
2. van 't Hof AW, Liem A, de Boer MJ, Zijlstra F.Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Zwolle Myocardial infarction Study Group. Lancet 1997; 350: 615-9.
3. Rolf Schröder. Prognostic impact of early st-segment resolution in acute ST-elevation myocardial infarction. Circulation 2004; 110: 506-10.
4. de Lemos JA, Braunwalo E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. J Am Coll Cardiol 2001; 38: 1283-94.
5. Schröder R, Dissmann R, Brüggemann T, Wegscheider K, Linderer T, Tebbe U, el al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol 1994; 24: 384-91.
6. Carlsson J, Kamp U, Härtel D, Brockmeier J, Meierhenrich R, Miketic S, et al. Resolution of ST-segment elevation in acute myocardial infarction--early prognostic significance after thrombolytic therapy. Results from the COBALT trial. Herz 1999; 24: 440-7.
7. Angeja BG, de Lemos J, Murphy SA, Marble SJ, Antman EM, Cannon CP, et al. Impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy. Am Heart J 2002; 144: 649-56.
8. Woodfield SL, Lundergan CF, Reiner JS, Greenhouse SW, Thompson MA, Rohrbeck SC, et al. Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience. J Am Coll Cardiol 1996; 28: 1661-9.
9. Mak KH, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox HD, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilizations of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arturs. J Am Coll Cardiol 1997; 30: 171-9.
10. Ishihara M, Sato H, Kawagoue T, Shimatani Y, Kurisu S, Nishioka K, et al. Impact of diabetes mellitus on long-term survival after acute myocardial infarction in patients with single vessel disease. Heart 2001; 86: 133-8.
11. Zairis MN, Lyras AG, Makrygiannis SS, Psarogianni PK, Adampoulou EN, Handanis SM, et al. Type 2 diabetes and intravenous thrombolysis outcome in the setting of ST elevation myocardial infarction. Diabetes Care 2004; 27: 967-71.
12. Hasdai D, Granger CB, Srivatsa SS, Crigor DA, Ellis SG, Gliff RM, et al. Diabetes mellitus and outcome after primary coronary angioplasty for acute myocardial infarction: lessons from the GUSTO-IIb Angioplasty Substudy. [Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes]. J Am Coll Cardiol 2000; 35: 1502-12.

13. Gray RP, Yudkin JS, Patterson DL. Enzymatic evidence of impaired reperfusion in diabetic patients after thrombolytic therapy for acute myocardial infarction. Br Heart J 1993; 70: 530-6.

14. Czyzk A, Krolewski AS, Szablowska S, A lot A, Kopczynski J, et al. Clinical course of myocardial infarction among diabetic patients. Diabetes Care 1980; 3: 526-9.

15. Timmer JR, Ottervanger JP, De boer M, Bocrsma E, Grines CL, Westerhout CM. Primary percutaneous coronary intervention compared with fibrinolysis for myocardial infarction in diabetes mellitus: result from the primary coronary angioplasty vs thrombolyis-2 trial. Arch Intern Med 2007; 167: 1353-9.

16. McGill JB, Schneider DJ, Arfken CL, Lucore CL, Sopel BG. Factors responsible for impaired fibrinolysis in obese subjects and NIDDM patients. Diabetes 1994; 43: 104-9.

17. Colwell JA, Nesto RW. The platelet in diabetes: focus on prevention of ischemic events. Diabetes Care 2003; 26: 2181-8.

18. King SB 3rd. Acute myocardial infarction: are diabetics different? J Am Coll Cardiol 2000; 35: 1513-5.

19. UCLA Chest Pain and Acute Coronary Syndrome,Patient Management Guideline. UCLA clinical practice guideline 2005.

20. Ratcliffe A T, Pepper C. Thrombolysis or primary angioplasty? Reperfusion therapy formyocardial infarction in the UK. Postgrad Med J 2008; 84: 73-7.