

THE IMPACT OF HYPERGLYCAEMIA ON MORBIDITY AND MORTALITY OF ACUTE CORONARY SYNDROMES AND ACUTE MYOCARDIAL INFARCTION

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Background: Though diabetes and hyperglycaemia are well known risk factors for morbidity and mortality associated with Coronary Heart Disease, there are no studies published from Pakistan on the impact of non-diabetic hyperglycaemia on these indices. The present study was undertaken to fill the gap in knowledge related to this aspect of hyperglycaemia in Pakistani patients. **Methods:** We studied 166 patients admitted to our coronary care unit from May 2008 to March 2009 with acute coronary syndrome and acute myocardial infarction. The patients were divided into three groups (a) Diabetic group (b) Impaired glucose group and (c) Normal glucose group according to the American Diabetic Association criteria. **Results:** It was observed that with increasing level of hyperglycaemia there was an increase in the mortality, with a *p*-value of 0.058. Hyperglycaemia was also associated with impaired left ventricular function and clinical evidence of left ventricular failure. Insulin therapy was under utilized and may have contributed to increased morbidity and mortality.

Keywords: Coronary artery syndromes, Myocardial infarction, Diabetes mellitus, Hyperglycaemia

INTRODUCTION

Diabetes mellitus is associated with an increased risk of cardiovascular morbidity and mortality,¹ and therefore as the prevalence of diabetes mellitus increases there will also be a corresponding increase in morbidity and mortality from cardiovascular disease.

The worldwide number of people with diabetes is expected to double in thirty years, increasing from 171 million in 2000 to 366 million in 2030. The largest percentage increase in numbers of patients will primarily be in Sub Saharan Africa and the Middle Eastern crescent. Significant increase will also occur in Asia (including India and China Latin America and the Carribean).²

The International Diabetes Federation gives an estimate of 12% prevalence in Pakistan with a total of 7–8.8 million people with diabetes in 2000, which is expected increase to about 14.5 million people by the year 2025.³ It is considered eighth in the world according to WHO estimation of prevalence of diabetes and by 2025 is expected to rise to fourth position.⁴

The incidence of diabetes mellitus in patients hospitalized with myocardial infarction ranges between 10–20%,⁵ and approximately 40% have impaired glucose levels.¹⁸

Patients with diabetes and myocardial infarction have greater incidence of major adverse cardiovascular events, higher in hospital and long-term mortality.⁵

The initial observation that elevated glucose is a common finding in patients with acute myocardial infarction was made more than forty years ago. Numerous studies have since established definitively that hyperglycaemia is highly prevalent

and that it is associated with increased risk of death and in hospital complications in patients with acute myocardial infarction. However, no uniform definition of hyperglycaemia in the setting of acute myocardial infarction exists. Six prior studies used various definitions and used glucose values ranging from 110 mg/dl to 200 mg/dl.

Several small studies from Pakistan are available which also suggest, increased mortality and worse in hospital outcome in diabetics as compared to the normal population^{7–10}

To our knowledge no study is available from Pakistan that has looked at hyperglycaemia in patients not known to be diabetics and its impact on morbidity and mortality of Acute Coronary Syndromes including acute Myocardial Infarction.

The purpose of this study was to determine the contribution of diabetes and hyperglycaemia to in-hospital morbidity and mortality in our patient population presenting with acute coronary syndromes (ACS) and Acute Myocardial Infarction.

MATERIALS AND METHODS

The study was carried out at the coronary care unit of Rehman Medical Institute, Peshawar from May 2008 to March 2009 and included 171 consecutive patients of coronary artery syndrome and acute myocardial infarction admitted to the coronary care unit during the study period.

Those with life threatening co-morbidities such as malignancy, end stage renal or liver disease, intracranial pathologies such as neoplasms, cerebral infarction or bleed were excluded.

Myocardial Infarction (MI) was defined by an increase in serum troponin I (higher than the upper

limit of hospital normal range) and clinical symptoms of ischemia and/or characteristic ECG findings. ST segment elevation MI was diagnosed when new ST segment elevation 1 mm or greater was seen in any location in two contiguous leads or when a new LBBB was found on the qualifying ECG. Unstable angina was diagnosed on the basis of typical anginal symptoms and ST segment depression on ECG and normal cardiac enzymes. Non ST segment elevation myocardial infarction (NSTEMI) was diagnosed on the basis of prolonged chest pain and elevated cardiac enzymes with or without ST segment depression.

Patients were considered diabetic if they had a history of diabetes, were on dietary control or medical management for diabetes, or if they had a fasting blood sugar of more than >126 mg/dl or a random blood sugar of >200 mg/dl on admission or during hospital stay. A fasting blood sugar of <100 mg/dl, random blood sugar <140 mg/dl were considered normal and those with fasting blood sugar between 100–125 and random blood sugar between 140–199 were considered to have impaired glucose tolerance.

There was no set protocol for the management of these patients, other than to follow the American college of cardiology (ACC) guidelines and were managed as advised by the admitting cardiologist. For all the admitted patients we obtained relevant data in the form of age, sex, history of comorbid conditions such as previous coronary artery disease, hypertension, smoking, hyperlipidemia, chronic renal disease and congestive cardiac failure. Their blood pressure and heart rate were noted at admission and clinical evidence of left ventricular failure was sought.

The laboratory workup included cardiac enzymes (CK-MB, Trop-I) admission blood sugar, lipid profile, blood urea and creatinine and chest x-ray. Wall motion abnormality and ejection fraction were determined by an echocardiogram. Coronary angiography and percutaneous coronary intervention (PCI) was performed when indicated and the extent of coronary disease recorded. All patients were followed up in the hospital.

Statistical analysis was performed using Chi-square and Student's *t*-test. Mortality was evaluated by using the Fisher test.

RESULTS

A total of 171 consecutive patients admitted to the CCU over a period of 10 months (May 2008–Mar 2009) were studied, five were excluded because of non-availability of blood sugar levels, leaving a total of 166 patients.

These patients were divided into three groups, normal glucose, diabetic and those with impaired glucose for study purposes according to the American Diabetic Association criteria for the diagnosis of diabetes. The number of normal glucose patients was 71, out of which 62 were diabetic and 33 fell into the Impaired Glucose category.

In the normal group there were 55 males and 16 females with an average age of 58.3 ± 10.8 years. Ten (14%) patients out of these had a previous history of myocardial infarction, angina, or CVA. One suffered from chronic renal failure, and 25 (35%) were hypertensive (Table-1).

Out of 62 diabetic patients the number of males and females were equal and the mean age of the group was approximately 56.5 ± 9.23 years. Out of these patients 24 (39%) had a previous history of myocardial infarction, angina, or CVA and 33 (53.2%) patients were hypertensive.

In the impaired group there were a total of 33 patients with an average age 55.2 ± 12 years. Six patients (18%) had a previous history of myocardial infarction, angina, CVA. One had chronic renal failure and 14 (42%) were hypertensive.

Out of a total of 166 patients, 102 (61.4%) presented with ST elevation myocardial infarction and 64 (38%) came into the NSTEMI/ACS category (Table-2). Only 8 (4.8%) presented within two hours of symptom onset, 57 (34.3%) patients presented between 2–12 hours duration, i.e., only a total of 39.1% patients sought medical attention within 12 hours of symptom onset and received lytic therapy in the form of streptokinase. The average time from onset of symptoms to arrival in hospital was 5.09 ± 4.31 hours and the average time to start of lytic therapy was 36.5 ± 27.5 minutes. Only five patients underwent primary PCI.

In the diabetic group there were a total of 28 (45.1%) STEMI, of whom 18 (29%) were anterior wall myocardial infarctions and 10 (16%) were inferior wall MI, 18 (29%) patients suffered NSTEMI and 18 (29%) were diagnosed as ACS.

There were a total of 25 (75.75%) STEMI in the impaired group with 13 (39%) anterior wall MI and 11 (33%) inferior MI and one posterior MI, 6 (18%) were diagnosed as ACS and 4 (12%) patients suffered from NSTEMI.

In the normal group 49 (69%) had STEMI with 16 (22%) anterior, 27 (38%) inferior and 6 (8.45) posterior MI. The NSTEMI were 16 (26%) and the ACS were 13 (18%) in the normal group of patients. There was no statistical difference between any of the groups.

Table-1: Demographics

Group	No.	Age	MI/Ang/CVA	CRF	Hypertension	Smokers	p-value
Diabetic	62	56.6±9.4	24 (39%)	-	33 (53%)	03 (4.8%)	N.S
Impaired Glucose	33	54.7±12.6	6 (18%)	1	14 (42%)	04 (12.12%)	N.S
Normal Glucose	71	58.3±10.8	10 (14%)	1	25 (35%)	14 (19.71%)	N.S

MI=Previous Myocardial Infarction; ANG=History of Angina; CVA=Cerebrovascular Accident; CRF=Chronic Renal Failure

Table-2: Location of infarction

Group	Ant MI	Inf MI	Post MI	NSTEMI	ACS	p-Value
Diabetic	18 (29%)	10 (16%)	0	18 (29%)	18 (29%)	NS
Impaired Glucose	13 (39%)	11 (33%)	1	04 (12%)	6 (18%)	NS
Normal Glucose	16 (22%)	27 (38%)	6 (8.4%)	16 (22%)	13 (18%)	NS

Ant MI=Anterior Wall Myocardial Infarction; Inf MI=Inferior Wall Myocardial Infarction; Post MI=Posterior Wall Myocardial Infarction; NSTEMI=Non ST Segment Elevation Myocardial Infarction; ACS=Acute Coronary Syndrome

Table-3: Evidence of left ventricular failure

Group	CXR	Clinical Evidence	p-Value
Diabetic	15 (24%)	26 (41%)	NS
Impaired Glucose	7 (21%)	12 (36%)	NS
Normal Glucose	9 (12%)	20 (28%)	NS

CXR=Chest X-ray; Clinical Evidence=Clinical Evidence of Left Ventricular Failure

Table-4: Echocardiogram

Group	MR	Wall Motion	Ejection Fraction			p-Values
			45-55	30-44	<30	
Diabetic	17 (27%)	39 (62%)	19 (30%)	27 (43%)	04 (6%)	N.S
Impaired Glucose	10 (30%)	23 (69%)	16 (48%)	10 (30%)	04 (12%)	N.S
Normal Glucose	32 (45%)	53 (74%)	33 (46%)	28 (39%)	04 (5%)	N.S

MR=Mitral Regurgitation; Wall Motion = Wall Motion Abnormality

Table-5: Drug therapy

Diabetic																		
	B-Blocker			Nitrates			Aspirin			ACE+ARB			Lipid Lowering			Clopidogrel		
	a	h	dx	a	h	dx	a	h	dx	a	h	dx	a	h	dx	a	h	dx
Total	11	46	42	8	56	50	14	61	52	6	43	40	10	60	52	6	56	48
%	17	74	67	12	90	80	22	98	83	9	69	64	16	96	83	9	90	77
Impaired Glucose																		
Total	0	24	21	2	31	28	3	31	27	2	19	19	1	30	27	1	30	25
%	0	72	63	6	93	84	9	93	81	6	57	57	1	90	81	1	90	75
Normal Glucose																		
Total	9	43	31	3	58	32	7	69	45	3	46	34	7	66	41	6	67	45
%	12	60	43	4	81	45	9	97	63	4	64	47	9	92	57	8	94	63

A=Before Admission to Hospital; H=During Hospital Stay; Dx=At Discharge

Out of the 62 diabetic patients 26 (41.93%) had evidence of left ventricular failure three of whom went on to develop cardiogenic shock (Table-3). The mean systolic and diastolic blood pressures in this group were 122 and 75 respectively and the average heart rate was 84 beats per minute.

In the impaired group a total of 12 (36%) patients had evidence of left ventricular dysfunction. Mean systolic blood pressure in this group was 117mm Hg and the mean diastolic blood pressure was 70mmHg. The average heart rate was 82 beats per minute.

In the normal blood sugar group left ventricular dysfunction was present in 20 (28%) patients, two of whom developed cardiogenic shock. The average systolic blood pressure of the group was 116mmHg and the average diastolic blood pressure was 75.5mmHg. The average heart rate of the group was 87.3 beats per minute.

In the diabetic group chest x-ray of 15 (24%) patients showed evidence of left ventricular dysfunction. In the impaired group 7 (21%) of the patients had abnormal chest X-rays indicating left ventricular failure and in the normal group 9 (12%) had chest X-ray evidence of left ventricular failure.

Coronary angiograms were carried out in 26 (41%) diabetic patients, 8 (12%) of whom then underwent PCI. In the impaired group 15 (45%) patients had an angiogram 6 (18%) of whom then underwent PCI. Coronary angiogram was performed on 37 (52%) normal patients and 16 (22%) of them underwent PCI.

In all three groups echocardiogram was performed. In the diabetic group wall motion abnormality was present in 39 (62%) patients, mild LV dysfunction was present in 19 (30%) patients, 27 (43%) patients had moderate impairment and severe LV impairment was present in 4 (6%) patients.

Seventeen (27%) of the diabetic patients had echocardiographic evidence of mitral regurgitation (Table-4).

Echocardiogram in the impaired group showed mitral regurgitation in 10 (30%) patients. Wall motion abnormality was present in 23 (69%) patients. Mild LV dysfunction was present in 16 (48%) patients, moderate dysfunction in 10 (30%) patients and severe LV dysfunction in 4 (12%) patients.

In the normal blood sugar group 32 (45%) patients had mitral regurgitation, wall motion abnormality was present in 53 (74%). There was mild LV dysfunction in 33 (46%) patients, moderate LV dysfunction in 28 (39%) patients and severe LV impairment in 4 (5%) patients.

Therapy given to all three groups was the same (Table-5). The in-hospital use of beta-blockers was 74% in diabetics, 72% in the impaired group and 60% in the normal blood sugar group and at discharge 67%, 63% and 43% received beta-blockers respectively. Nitrate use was 90% in the diabetic group, 93% in the impaired group and 81% in the normal sugar group and at discharge the use was 80%, 84% and 45% respectively.

Aspirin was used in 98% diabetics, 93% patients with impaired glucose and 97% of the normal sugar patients and at discharge the use was 83%, 81%, 63% respectively. ACE inhibitors were used in 69% diabetics, 57% of the impaired group and 64% of the normal blood sugar group and at discharge the percentage use was 64%, 57% and 47% respectively.

Lipid lowering therapy was given to 96% diabetics, 90% of the impaired group and 92% of the normal sugar group and at discharge the figures were 83%, 81%, 57% respectively. In-hospital use of clopidogrel was 90%, 90% and 94% and at discharge it was 77%, 75% and 63% in the diabetic, impaired and normal sugar group respectively.

In the diabetic group the length of hospital stay was 4.11 ± 2.99 days. The mean length of stay of the impaired group was 3.88 ± 2.69 days and of the normal sugar group was 4.46 ± 3.51 days.

The mortality of the diabetic group was 9.6%, 6.06% in the impaired group and 5.6% in the normal sugar group with a *p*-value of 0.058.

DISCUSSION

Compared to the West, our patients of acute coronary syndromes/myocardial infarction presented at a younger age. The average age of the diabetic population was 56 years. The age of the impaired group was 54 years and that of the normal group was 58 years. The Western population is older, the age of the diabetic group is around 65 years or more, the

average age of the normal group is around 60 years and the impaired group lies between the two.^{11,12}

Hypertension was a risk factor that was found in a significant number of our study population. In the diabetic group the prevalence was slightly lower at 53% as compared to 60% reported in various studies from the west, similar differences were found in the impaired group with 42% prevalence in our population as compared to 51% in the West.

In our normal group of patients 35% were hypertensive as compared to the Western reported figures of around 40–45%.^{11,13,14}

In our study population we observed an admission hyperglycaemia of 57.2% comparable to 51–58% noted in the largest observational studies from the west.⁶

We observed a much higher prevalence of diabetes (37%) in our study group as compared to the 12–26% prevalence reported from the West.^{15,5} This is because South Asians have been observed to have a risk of developing diabetes at lower levels of body mass index than western population.³

There was no significant difference in the location of the infarction. Majority of the patients sustained an anterior wall myocardial infarction; the second most common type observed was an inferior wall infarction. The number of NSTEMI and ACS were similar in all three groups.

An important observation was the late presentation of majority of the patients, only 39% of the patients presented with in 12 hours of symptom onset. The main reason for this being the lack of adequate emergency services available to the general population, long distances that the patients have to travel to reach a tertiary care facility. The main problem is the delay in seeking medical attention. It was observed that once the hospital is reached initiation of treatment is quite prompt, all the patients received lytic therapy in the form of streptokinase, with in half an hour of arrival to hospital.

Only five out of a total of 166 patients underwent primary PCI. Coronary angiograms were performed in 41% of the diabetic patients, 45% with impaired glucose and 52% of the normal patients, however the rate of revascularization by PCI was only between 12–22%. The major reasons for this very low rate of revascularization both primary and secondary are the lack of financial affordability of the general population, the non availability of medical insurance to the public. In addition, 24 hour/7 days a week coronary angiography and angioplasty facilities are not available.

We assessed the morbidity of these patients using clinical evidence of left ventricular failure and echocardiographic parameters such as LV ejection

fractions and wall motion abnormality. The association between hyperglycaemia and ejection fraction achieved near significance ($r = -0.164$, $p = 0.052$) A reduction in the ejection fraction was observed with the increasing hyperglycaemia, an observation similar to that reported by the western studies.¹⁴

Clinical evidence of left ventricular failure was more as the level of hyperglycaemia increased; also greater wall motion abnormalities were observed with increasing levels of hyperglycaemia, observations similar to the western data.¹⁶⁻¹⁸ However, both these observations did not reach statistical significance possibly because of the small sample size of the study group.

The mortality of our study population was comparable to the western figures. Our diabetic population showed a 9.6% mortality comparable to the western figures of 8.2-10%.^{1,5} We had a 5.6% mortality in the normal group similar to 1.7-5%^{1,5} reported from the western population. Intergroup comparison showed a trend towards increasing mortality with increasing blood sugar levels $p = 0.058$ however this observation did not reach statistical significance. A larger study group would probably have given us more definitive result.

The drug therapy received by patients was according to the international recommendations; the most commonly used medications were aspirin, clopidogrel and statins, with over 90% in hospital use and over 70% use at discharge. In hospital use of nitrates was 88%, 56% of whom were also sent home on nitrates indicating a trend of increased use in our setting. Beta blockers and ACE inhibitors were also used routinely however there is still room for improvement where their use is concerned.

Insulin therapy was under-utilized with only 50% diabetics treated with insulin during hospital stay and a very small percentage of the impaired group (9%) received in hospital insulin therapy, a finding similar to that observed in the Western data.⁶

Glycoprotein IIb, IIIa inhibitors were rarely used because of the non-affordability by our patient population. Some drawbacks of the study were evident. The study population was calculated on the assumption that approximately 30% patients would be diabetic and an equal number would have impaired glucose tolerance. However the number in the impaired glucose was much smaller at about 20% and the diabetic group was larger at 37%. A larger study population may have contributed to statistically conclusive results.

The patients included in the study were not treated in a uniform protocol defined manner and hence discrepancies in treatment could have influenced the outcomes. However, the above

drawback would be offset by the benefit of enrolling patients as we did where the outcome could be compared with other such studies from other countries. In other words the actual outcomes of our hospital, in a non-protocol defined treatment model as compared to western studies.

A longer follow up of at least 30 day mortality would have added significantly to the information on the subject. However, follow up at our institution is poor and it was felt that the drop out rate would be very high and hence not very useful.

To conclude, our data are in agreement with that reported from the west where an increase in the blood sugar is associated with an increased in hospital mortality although the p -value (0.058) in our study was close to significance. Similarly there was good correlation between an elevated blood glucose level and impaired left ventricular dysfunction on echocardiography and clinical evidence of left ventricular function.

In our study there was a marked delay in the time of onset of symptoms and arrival of the patient in the emergency room. Only 39% appeared in 12hrs. In the west the average arrival time would be about 2hrs. These obvious differences are due to the very effective emergency services in the west and their non-existence in our country.

It seems that in hospital use of insulin therapy for elevated blood glucose levels was very poor but similar to the west.

Drug therapy in the diabetic and impaired glucose group appears to be similar to other studies but in the normal group was under utilized. Reasons for this above discrepancy are not clear from the present study. It would therefore be appropriate to postulate that as a high glucose level in the setting of acute infarction and ACS correlates with a higher morbidity and mortality, reduction of the glucose level with insulin therapy would reduce the above adverse effects. A larger multi-centre trial to test the above hypothesis would be desirable.

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