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Observational Study

The Association of Hyperglycaemia with Complications in Patients with Acute Myocardial Infarction-An Observational Study

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Abstract

Background: Acute myocardial infarction (AMI) is one of the most common causes of morbidity and mortality globally. It occurs when myocardial ischemia, the diminished blood supply to the heart, exceeds a particular threshold and saturates the myocardial repair mechanisms capacity to maintain normal function and homeostasis. Furthermore, the presence of hyperglycaemia substantiates electrophysiological alteration, impairs left ventricular (LV) function and causes perfusion defects promoting multiple cardiac complications viz. arrhythmias, cardiogenic shock, heart failure and death. Raised admission random blood sugar (RBS) signifies hyperglycaemia and HbA1c serves a prognostic purpose in patients of myocardial infarction (MI) to be watchful regarding complications.

Aim: The present study was carried out to study the association between admission blood glucose levels and the development of complications in patients having acute MI. We also studied the association of HbA1c levels with prognosis in MI patients.

Materials and Methods: 100 eligible consecutive patients of acute myocardial infarction (AMI) were enrolled and were grouped according to their RBS whether <180 mg/mL (group 1) or >180 mg/mL (group 2) irrespective of prior history of diabetes. In a parallel scenario, these 100 patients were also evaluated for HbA1c levels and divided whether <6% (group 1) and >6% (group 2) and analysed using particle enhanced immune-turbidimetric test. Simultaneously, routine investigations viz., complete blood count, renal and liver profile, 2D echo and serial electrocardiogram (ECG) were performed.

Results: Biophysiological processes involving renin-angiotensin-aldosterone system (RAAS) activation, sympathetic modalities and inflammatory cascade due to AMI induced stress potentiates reactionary hyperglycaemia which evidently showed more risk of complications, thereby developing heart failure in 36% cases (group 2) contrasting 6% (group 1). Further, arrhythmias occurred in 30% (group 2) contrasting 6% (group 1) and shock in 26% (group 2) with 6% (group 1). Hyperglycaemia was associated with higher mortality viz., 28% (group 2) in comparison to 6% (group 1) with a significant difference. The HbA1c levels underlined higher complications viz., 23.1% (group 2) than 12.5% (group 1) with overall mortality higher in diabetics (group 2) in comparison with non-diabetics.

Conclusion: The study tends to highlight the stress response initiated by a myocardial injury that triggers proinflammatory cascades and sympathetic nervous system; causing catecholamine secretions and pseudo-emergency states thus causing extensive myocardial damage and further deterioration in prognosis.

Keywords: Hyperglycaemia, myocardial infarction, cardiac arrhythmias, blood sugar, heart failure

Introduction

Ischaemic heart disease (IHD) causes more mortality and greater economic costs than any other illness in the developed world. Cardiovascular diseases as of 2018 were the leading cause of death globally resulting in over 17.6 million deaths yearly worldwide in which IHD contributed 43.2% deaths and is expected to climb to more than 23.6 million by 2030.[1] Acute myocardial infarction, as a component of IHD, is a condition in which there are an inadequate blood and oxygen supply to a portion of the myocardium; typically presents when an imbalance occurs between myocardial oxygen supply and demand, most commonly due to atherosclerosis of an epicardial coronary artery (or arteries).[2,3]

The incidence of MI rises with atherosclerotic disease mainly predisposed by six primary risk factors viz. diabetes mellitus (DM), hypertension, tobacco use, dyslipidaemia, male sex and family history of arterial atherosclerosis.[4] Occurrence of myocardial ischaemia characterised mainly by cell death, takes variable duration depending upon the presence of collaterals to the ischaemic zone, persistent or intermittent coronary arterial occlusion, the myocytic sensitivity to ischaemia, pre-conditioning or finally, individual demand for myocardial oxygen and nutrients.

From a morphological viewpoint, the two types of MI are transmural and non-transmural, whereas on the basis of electrocardiographic findings are ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI).[5] Diagnosis is confirmed by ECG, serum cardiac biomarkers, cardiac imaging, and nonspecific indices of tissue necrosis and inflammation. If untreated, the ischemia worsens manifesting as reduced ventricular compliance (diastolic failure) and/or a reduced stroke volume with secondary cardiac dilation (systolic failure) producing cardiogenic shock (hypotension refractory to volume resuscitation with features of end-organ hypoperfusion due to myocardial damage) and heart failure viz. chronic progressive condition where heart falls unable to pump blood enough to meet bodily demands.[6-8] Additionally, MI causes the ventricular wall or papillary muscle rupture leading to mitral regurgitation or pseudoaneurysms.[9] Arrhythmias viz. change from the normal sequence of electrical impulses e.g., ventricular flutter and fibrillation and sudden cardiac death are other noted complications.[10,11]

Hyperglycaemia due to pre-existing, but undetected type 2 diabetes mellitus (DM), impaired glucose tolerance, or existing insulin resistance contribute to worse outcomes post-MI, where DM is proclaimed as a group of metabolic diseases characterised by hyperglycaemia due to defective insulin output, action or both.[12] It causes pronounced sympathetic nervous system activation and catecholamine secretion; predisposes to arrhythmias with QT prolongation.[13] Marfella R *et al.* showed acute hyperglycaemia produces significant increments of QTc and QTc dispersion in normal subjects.[14] Raised RBS causes pump failure and abolishes the response protective mechanisms viz. "ischemic preconditioning" which shields against myocardial ischemic insult and ischemia-reperfusion injury.[15,16] Hyperglycaemia embraces higher free fatty acid concentrations, insulin resistance and impaired myocardial glucose utilization.[17,18] It induces enhanced T cell activation, both cluster of differentiation 4 (CD4) and CD8 with elevated levels of C-reactive protein, interleukin-6, interleukin-18 and tumour necrosis factor (TNF) potentiating plaque instability.[19,20]

This delineates hyperglycaemia as a well-recognized pathogenic process for atherosclerosis and cardiovascular disease including free radical production and exhibiting lower tissue plasminogen activator activity causing increased platelet aggregation.[21]

This study aims to evaluate hyperglycaemic effects in patients already suffering from acute coronary syndromes (ACS) as a predictor of poor associated prognosis for it being adjoining comorbidity and increased risk of in-hospital complications in patients both with and without DM.

Materials and Methods

This is a hospital-based observational - analytical study conducted in Sawai Man Singh (S.M.S) Hospital, Jaipur, Rajasthan, India between June 2019 to February 2020, aimed at estimating admission RBS and HbA1c in patients of acute MI and to assess the complications arising in these patients till the time of discharge.

100 consecutive patients presenting with AMI on day 1 in departments of medicine and cardiology, between 40 to 80 years irrespective of sex, were taken. 50 of them with admission RBS <180 mg/mL were included in the study (group 1) and 50 with admission, RBS >180 mg/mL were included in the study (group 2) irrespective of prior history of diabetes after applying the inclusion and exclusion criteria [the level 180 mg/mL as per the Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study].[22] All patients exhibiting typical rise and gradual fall of the cardiac

biomarker of myocardial necrosis (cardiac troponin), confirmed using troponin T (Trop-T) (>0.017 IU/L) and creatine kinase myocardial band (CPK-MB) (>25 IU/L) values, as found raised, with at least one of the criteria including ischemic symptoms or development of pathological Q-waves or new significant ST-segment/T-wave changes or new left bundle branch block (LBBB) in ECG; were included in the study. Furthermore, patients with comorbidities like renal or hepatic insufficiency, trauma, major surgery or other cardiovascular deteriorations such as aneurysms, pericardial effusion, myocarditis and valvular heart diseases were excluded from the study. Before participation in this study, written informed consent was obtained from all the subjects.

Serum glucose and HbA1c levels were measured along with simultaneous routine investigations like serial ECG, 2D ECHO, hepatic and renal profile and delineation of systolic (SBP) and diastolic blood pressure (DBP).

The patients were then followed for vitals, major events and complications like arrhythmia, heart failure, shock and death during the hospital stay.

Statistical Analysis

All data were entered on MS Excel sheet and statistical analysis carried out using statistical software PRIMER and Med Calc.14.2.1.0. The qualitative data were expressed in proportion and percentage. The difference in proportion was analysed by using the chi-square test. The quantitative data were expressed in mean and standard deviation**.** Student `t' test was used to infer the difference in means.

Correlation analysis was done by using the Pearson's correlation coefficient and multivariate linear regression was performed. Significance for tests was determined as 95% ($p<0.05$). Development of complications was compared between two study groups and correlated with HbA1c levels**.**

Results

The study enrolled 100 patients who were then evaluated based on multiple factors viz., age, sex, body mass index (BMI), smoking status, h/o DM and hypertension, which were then compared for significance.

Table 1 shows the mean age in group 2 was slightly higher (62.26 years) as compared to group 1 (62.22 years, but the difference was not statistically significant ($p>0.05$).

Table 1. Comparing the demographic profile and risk factors of the study groups. Abbreviations: DOF- Degrees of freedom; MV- Multivariate; NS- Non-significant; S- Significant; SBP- Systolic blood pressure; DBP- Diastolic blood pressure. A p-value of less than 0.05 was considered statistically significant.

Variables	Group 1 (G1)	Group 2 (G2)	Mean value	Standard deviation	Test value	DOF	p-value (MV)
Age (years)	50	50	(G1) 62.28	8.913	0.028	98	0.07
			(G2) 62.26	4.38	t value		NS
Gender							
Male	18	20			0.042	1	0.84
Female	20	30			chi value		NS
BMI (kg/m^2)	50	50	(G1) 26.39	4.218	0.065	98	0.51
			(G2) 25.84	3.867	t value		NS
Smoking status							
No	28	21			1.441	1	0.27
Yes	22	29			chi value		NS
H/o Diabetes							
No	37	32			0.718	1	0.032
Yes	13	18			chi value		S
H/o Hypertension							

Variables	Group 1 (G1)	Group 2 (G2)	Mean value	Standard deviation	Test value	DOF	p-value (MV)
No	30	22			0.56	1	0.04
Yes	20	28			chi value		S
Mean heart rate	50	50	(G1) 84.94	24.52	3.325	96	0.001
Heart rate			(G2) 111.8	50.91	t value		S
SBP	50	50	(G1) 126.4	28.39	2.709	98	0.007
			(G2) 108.6	36.91	t value		S
DBP	50	50	(G1) 89.44	23.87	2.775	98	0.004
			(G2) 79.24	27.19	t value		S
Mean resp. rate	50	50	(G1) 17.48	4.487	-4.383	98	<0.001
			(G2) 22.04	5.831	t value		S

Gender wise group 1 had more males (64%) as compared to group 2 (60%) and the mean BMI in group 1 (26.39 kg/m^2) is slightly higher in contrasting group 2 (25.84 kg/m^2), but the differences were statistically insignificant (p>0.05).

Table 1 defines the risk factors including smoking status showing that 29 (58%) subjects in group 2 were smokers, whereas only 22 (44%) in group 1 were smokers. H/o diabetes was more in group 2 (36%) contrasting group 1 (26%) and h/o hypertension (BP >140/90) was higher (56%) in group 2 as compared to group 1 (40%) when taken for multivariate analysis proved statistically significant (p<0.05), establishing them as independent risk factors for complicating MI prognosis.

The mean heart rate was comparatively higher in group 2 (111.8/min) contrasting group 1 (84.94/min) which was statistically significant (p=0.001). The mean SBP was higher in group 1 (126.4 mmHg) vs. group 2 (108.6 mmHg). Further, the mean DBP was more in group 1 (89.44 mmHg) contrasting group 2 (75.24 mmHg) and both were found to be statistically significant (p<0.05).

Also, the mean respiratory rate in group 2 (22.04/min) was higher than group 1 (17.48/min) which too was statistically significant (p<0.001).

Overall, these observations revealed that the two groups were comparable taking into account all the confounding factors. There were pre-existing hypertension and concurrent diabetes in maximum patients of group 2 respectively that predisposed them to subsequently cause comorbidities and as expected, suggested them to independently deteriorate the patient viability.

Table 2 delineates that adversities like basal crepitations were observed more frequently in group 2 (36%) as compared to group 1 (8%). Presence of S_3 gallop was found in 34% of group 2 subjects and 6% of group 1 subjects where both these differences were statistically significant (p<0.05). Bilateral pedal oedema occurred more in group 2 subjects (8%) as compared to group 1 subjects (4%) but was statistically insignificant (p>0.05). Furthermore, heart failure as a complication was seen in 36% group 2 subjects and only 8% group 1 subjects which were statistically significant (p<0.05).

Multiple arrhythmias and cardiogenic shock were reported in 30% group 2 subjects each, detected on cardiac monitoring, contrasting only 6% cases in group 1 and the difference was statistically significant (p=0.004).

Table 3 signifies HbA1c and its statistically significant differences in the complication of AMI (p<0.001). It reveals that death as an outcome occurred in 17.3% group 2 subjects and 16.7% group 1 subjects but revealed to be statistically insignificant (p>0.05). In-hospital management was given as per the American Heart Association (AHA) guidelines including drugs viz., metoprolol and statins viz., atorvastatin usage for patient recovery.

Low dose aspirin was given both prophylactically and therapeutically and all feasible revascularizations were carried out while simultaneous response on improvement and complications was monitored and documented.

Table 2. Comparison and analysis of the complications of AMI. Abbreviations: DOF- Degrees of freedom; NS- Non-significant; S Significant.

Complications	Group 1	Group 2	Test value	DOF	p-value
Basal crepitations	Chi-square				
No	46	32	9.848	1	0.002
Yes	4	18			S
S_3 gallop					
No	47	33	10.562	1	0.001
Yes	3	17			S
Jugular venous pressure					
Increased	2	11	5.659	1	0.017
Normal	48	39			S
Pedal oedema					
No	48	46	0.157	1	0.692
Yes	2	4			NS
Heart failure					
Yes	4	18	9.848	1	0.002
No	46	32			S
Arrhythmias					
Yes	3	15	8.198	1	0.004
No	47	35			S
Cardiogenic shock					
Yes	3	11	4.07	1	0.044
No	47	39			S
Final outcome					
Death	3	14	7.087	1	0.008
Survived	47	36			S

Table 3. Prognostic value of HbA1c on variable outcomes. Abbreviations: HbA1c- Haemoglobin A1c; RBS- Random blood sugar; DOF- Degrees of freedom; NS- Non-significant; S- Significant.

Differentials	Group 1	Group 2	Mean value	Standard deviation	Test value	DOF	p-value
HbA1c (mean)	48	52	(G1) 5.829	0.6998	-4.619	98	<0.001
			(G2) 7.015	1.675	t value		S
RBS (mean)	48	52	(G1) 119.52	32.78	10.818	98	<0.001
			(G2) 237.14	69.54	t value		S
Arrhythmias							
Yes	6	12			1	1	0.265
No	42	40			chi value		NS
Cardiogenic shock							
Yes	5	8			0.194	1	0.66
No	43	44			chi value		NS
Heart failure							
Yes	9	13			0.262	1	0.609
No	39	39			chi value		NS
Final outcome							
Death	8	9			0.033	1	0.856
Survived	40	43			chi value		NS

Discussion

In our study regarding the association of admission RBS and HbA1c with complications in the patients of acute MI, it was observed that complications such as heart failure, shock, arrhythmias and demise did occur. Mainly, failure was present in 8% of group 1 patients while it was 36% in group 2 patients. This was significant (p=0.002), indicating incidence of heart failure is more in the group with higher RBS, where known diabetics formed a major proportion.

Clinical findings like basal crepitations, S_3 gallop, jugular venous pressure (JVP) and pedal oedema were also compared, which suggested a significant difference highlighting the higher incidence of heart failure in group 2. It was recorded that arrhythmias and cardiogenic shock occurred more frequently with higher blood sugar as in group 2. Mortality was only 6% in group 1, whereas was 28% in group 2 patients with a p-value of 0.008, indicating highly significant difference attributed to hyperglycaemia.

Prognostic role of raised RBS in AMI has been validated by many studies e.g., Milvidate *et al*. who studied the frequency of admission hyperglycaemia and abnormal glucose tolerance at discharge in patients with acute MI and no previous h/o DM and the results proved in concordance to our results.[23] Mansour *et al*. studied regarding hyperglycaemia on arrival for patients presenting with ACS, irrespective of diabetic status and concluded using logistic regression with heart failure as the dependent variable attributed to admission acute phase hyperglycaemia (OR=2.1344, 95% CI=1.0282-4.4307; p=0.0419) comparable to ours where AMI led to 30% of cases of heart failure.[24]

Higher mortality rates viz. 28% in hyperglycaemic patients were recorded in our study; similar to Meier *et al.* which showed higher long-term mortality rates and larger infarct size (measured by creatine kinase and MB fraction levels) among 116 hyperglycaemic AMI patients with 18% mortality.[25]

Interestingly, Oswald and Smith *et al*. in their two studies assessed the prevalence of undiagnosed DM (using HbA1c) in patients admitted with AMI and the effect of DM on outcomes and reported 33% mortality (>7.5%) and 63% (>8.5%) whereas it was 18% in our observations correlated with HbA1c >6%.[26]

In our study, multiple confounding risk factors showed statistically no significant differences between the groups depicting the comparable composition of the groups.

Zaghlaa *et al.* assessed the impact of admission RBS on the hospital course and outcome in patients presenting with AMI in the intensive care unit (ICU) with 50 cases and elaborated that there was a significant correlation between RBS and h/o DM and h/o smoking (p=0.000 and 0.008, respectively) and also between RBS and complications of MI including sinus tachycardia, arrhythmia, and ICU length of stay (p=0.008, 0.002, and 0.000, respectively); which was statistically significant on multivariate regression, even in our study (p<0.05 each, respectively). In the HbA1c prognostic scenario, 12.5% patients developed arrhythmia in group 1 and 23.1% patients in group 2, whereas cardiogenic shock was present in 10.44% patients in group 1 while 15.45% of patients in group 2 and both differences were insignificant (p>0.05).[27]

Lazzeri *et al.* assessed the prognostic role of HbA1c for mortality at short and long terms in 518 consecutive STEMI patients without h/o DM and observed that higher HbA1c values pinpoint a subset of patients who, in the early phase of STEMI, show an abnormal glucose response to stress indicated by dysglyceamia, worse glycaemic control during intensive cardiac care unit (ICCU) stay (peak glycaemia) and a higher incidence of acute insulin resistance (homeostatic model assessment index) in comparison to the evident complications of AMI that raised glycated Hb predisposed to.[28]

The comparative analysis in our study thereby showed that elevated RBS in patients with AMI appears more important than prior long-term abnormal glucose metabolism (detected by elevated HbA1c) in predicting outcome in patients with AMI and this may be because of a stress response accompanied by high levels of catecholamines and cortisol which increase glycogenolysis and lipolysis and reduce insulin sensitivity, resulting in elevated glucose levels.

Therefore, hyperglycaemic patients due attributed to that response; cause more severe haemodynamic compromise or more extensive myocardial damage thereby worsening the prognosis.

Limitation of the Study

Our study has a limitation of one-time glucose estimation irrespective of timing and previous meals which may vary in normal individual also.

Conclusion

We know that IHD is a common cause of death worldwide and is likely to become the most common cause of death globally by 2020. Our comparative analysis showed elevated glucose or stress hyperglycaemia common in AMI patients and RBS as an important predictor of adverse outcomes.

This observational study aimed at highlighting the importance of measuring serum glucose levels as a viable indicator of further morbidities in an already morbid state of MI using advanced modalities viz., spectrophotometry for glucose and immune-turbidimetric tests for HbA1c levels and highlights the clear-cut difference in occurrence and incidence of cardiovascular complications in hyperglycaemic patients suffering from MI thus establishing a positive association between the two factors.

Declaration of conflicting interest

The author declares the absence of any conflict of interest.

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Ethical approval

Since the study is an observational study, there is no need for any ethical committee approval.

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