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ROLE OF GLYCOSYLATED HEMOGLOBIN (HBA1C) IN DIABETICS PRESENTING WITH ACUTE MYOCARDIAL INFARCTION (AMI) ON B-TYPE NATRIURETIC PEPTIDE (BNP) AND ITS CORRELATION WITH LEFT VENTRICULAR FUNCTIONS

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ASK,MH,SR conceived the idea, planned the study and critically revised the manuscript. AA helped in data collection and statistical analysis. All authors contributed significantly to the submitted manuscript.

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ABSTRACT

Objective: To determine the effect of glycosylated hemoglobin (HbA1c) on the left ventricular (LV) functions and plasma B-type natriuretic peptide (BNP) levels in type 2 diabetic patients (T2DM) who presented with acute myocardial infarction (AMI).

Methodology: This cross-sectional study was conducted on patients with previously known T2DM admitted after first episode of AMI in department of cardiology, Lady Reading Hospital (LRH) and Rehman Medical Institute (RMI), Peshawar from 1st November 2014 to 30th June 2015. Subjects were dichotomized on the basis of admission HbA1c; HbA1c $\leqslant$ 7% was taken as optimal control group and HbA1c > 7% was taken as suboptimal control group.

Results: A total of 196 patients were included in the study. About 35(17.85%) subjects had optimal glycaemic control, compared to 161 (82.15%), who had suboptimal glycaemic control. BNP levels were significantly higher in suboptimal control group compared to optimal group (351.8±419.46 pg/ml vs 567.2±444.35 pg/ml, p = 0.009). A negative correlation between HbA1c and ejection fraction (r = -0.3, p = <0.00 for optimal control group and r = -0.4, p = 0.01 for suboptimal control group) and between HbA1c and fractional shortening (r = -0.4, p = 0.01 for optimal control group and r = -0.3, p = <0.00 for suboptimal control group) was found.

Conclusion: This study suggests that HbA1c has significant impact on plasma BNP levels and optimal HbA1c levels in Type 2 diabetic patients result in improved LV systolic functions after AMI.

Key Words: Glycosylated Hemoglobin, B-Type Natriuretic Peptide Left ventricular functions, Type 2 diabetes mellitu, optimal glycemic control, suboptimal glycemic control.

INTRODUCTION

Acute myocardial infarction (AMI) is the most prevalent and life threatening emergency and is responsible for 7.3 million deaths per year worldwide which is 42% of all cardiovascular deaths.[1] In United States, 1.5 million men suffer from AMI every year.[2] Of these, 71.4% are those who suffer AMI for first time and 28.6% are those who already had one or more episodes of AMI in their life.[3] In Pakistan, 5.09 million people suffered from AMI in 2009.[4]

Diabetes mellitus (DM) is an established and independent risk factor for AMI. DM magnifies the risk of AMI about 5-fold.[5] It is also estimated that 80% of the deaths among diabetic patients are due to cardiovascular diseases.[6] The magnitude of its effect varies by age, sex and presence of other risk factors but the critical gap in the knowledge is whether high blood sugar is the mediator or marker of adverse outcome.[7,8] In addition, the influence of optimal glycemic control (HbA1c $\leqslant$ 7%) on the LV functions in diabetics presenting with AMI has not been clearly defined. There are conflicting theories suggesting opposite outcomes. Some clinical studies have proved that hyperglycemia does not affect the outcome. Rather, it results in tachycardia and increases cardiac output.[7] On the other hand, cardiac remodeling studies have shown that concomitant T2DM and AMI results in severely impaired LV functions such as left ventricle end diastolic diameter (LVEDd), left ventricle end systolic diameter (LVESd), fractional shortening (FS) and ejection fraction (EF).[9] Therefore the present study was intended to investigate influence of HbA1c on plasma BNP levels and LV functions after AMI in type 2 diabetic patients and to access level of stress on the left ventricular myocardium wall due to infarction by measuring HbA1c and BNP and recording the values of echocardiographic findings (LVEDd, LVESd, FS, and EF)in diabetic patients who presented with MI.

METHODOLOGY

This was a cross sectional study in which blood samples and data were collected from type 2 diabetic (T2DM) patients who were admitted for AMI treatment in department of cardiology, Lady Reading Hospital (LRH), Peshawar and cardiology department of Rehman Medical Institute (RMI), Peshawar from 1st November 2014 to 30th June 2015 with the consent of respective in-charges of departments. Ethical approval for this study was obtained from Khyber Medical University (KMU) Ethics Board.

T2DM patients who had first episode of AMI and had received thrombolytic treatment within 12 hours of onset of chest pain were included in this study. Those type 2 diabetic patients who had first AMI but refused to give informed consent or had previous history of MI or coronary artery bypass surgery or valvular or myopathic heart disease were not included in this study. In the present work, DM was defined as the use of anti-diabetic agents (oral hypoglycemic medicines or insulin or both) at the time of admission or the patients having documents containing laboratory results of previous HbA1c test compatible with the diagnosis of diabetes according to American Diabetes Association (ADA) guidelines or documentation related to history of diabetes mellitus. The admission glucose was not accounted as a criterion for the diagnosis of T2DM as it may be affected by stress factor. The duration of DM was also not taken into consideration. The subjects were dichotomized on the basis of glycemic control. The cut-off value for good or optimal glycemic control was taken as diabetic patients with mean HbA1c $\leqslant$ 7% and for poor or suboptimal glycemic control was taken as diabetic patients with mean HbA1c $>$ 7%. These values are in accordance with the current definition by American Diabetes Association (ADA) guidelines at the time of this study. The diagnosis of AMI was based on guidelines presented by third Global MI Task Forces. The short-term outcomes were measured by recording the echocardiographic findings (LVEDd, LVESd, fractional shortening and ejection fraction) and measuring plasma BNP levels. In addition, variables like age, gender, anthropometric measurements (height and weight for BMI calculation), patient's systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were also recorded.

Blood samples were taken and analyzed for glycosylated hemoglobin (HbA1c) using Fast ion-exchange resin separation technique using End-point method and for BNP levels by chemiluminescentmicroparticle immunoassay (CMIA) method.

Continous variables were recorded in mean and standard deviation. Categorical variables were described as frequency and percentages. All data of different variables were entered into the computer on regular basis and processed by using SPSS (statistical package for social sciences) software version 16.

RESULTS

A total of 196 diabetic subjects from of either gender were included in the work undertaken. There was no significant difference between optimal and suboptimal groups in terms of demographics and vital signs on admission.

In suboptimal control group, plasma BNP levels were significantly higher compared to optimal control group (567.2$\pm$444.35 pg/ml vs 351.8$\pm$419.46 pg/ml, p = 0.01). Similarly, there was significant difference between optimal and suboptimal control group in terms of LVESd (37.3$\pm$8.59 mm vs 41.3$\pm$9.24 mm, p = 0.02), fractional shortening (27.2$\pm$6.70 % vs 23.5$\pm$6.84%, p = 0.01) and ejection fraction (53$\pm$10.46 % vs 45.8$\pm$9.33 %, p = $<$0.00) as shown in Table 1.

Table 1: Baseline Characteristics of the Study Groups (n=196)

Variables	HbA1c = 7% n = 35	HbA1c > 7% n = 161	p-value
Demographics			
Age (Mean ±SD) years	59.9±5.58	59.4±7.95	NS
Gender, n (%)			
Male	20 (57.14)	96(59.62)	NS
Female	15 (42.86)	65(40.38)	NS
Vital Signs on admission, (Mean ±SD)			
Heart rate (beats per minute)	91.7±10.00	92.8±11.44	NS
Systolic Blood Pressure (mmHg)	156.5±39.10	154.8±33.85	NS
Diastolic Blood Pressure (mmHg)	86.0±24.39	85.1±22.64	NS
Laboratory Results , (Mean ±SD)			
HbA1c(%)	6.67±0.18	8.65±0.98	<0.00
BNP (pg/ml)	351.8±419.46	567.2±444.35	0.01
Echocardiographic results of left ventricular systolic functions , (Mean ±SD)			
Left ventricle end diastolic diameter (LVED d) (mm)	51.8±8.74	54.3±10.62	0.195
Left ventricle end systolic diameter (LVESd) (mm)	37.3±8.59	41.3±9.24	0.02
Fractional Shortening (%)	27.2±6.70	23.5±6.84	0.01
Ejection Fraction (%)	53.0±10.46	45.8±9.33	<0.00

Subjects in both groups were divided into subgroups according to their ejection fraction (EF); Group 1- severe LV dysfunction (EF < 30%), Group 2- moderate LV dysfunction (EF = 30-44%), Group 3- mild LV dysfunction (EF = 45-54%) and Group 4- preserved LV function (EF ⩾ 55%). There was significant difference between optimal and suboptimal control groups in all four groups (Group 1: 5.71% vs 7.51%, p = 0.02; Group 2: 14.28% vs 32.29%, p =< 0.00; Group 3: 31.42% vs 49.06%, p < 0.00 and Group 4: 48.57% vs 11.18%, p =<0.00) as shown in Table 2.

Table 2: Ejection Fraction Distribution of the Study Groups (n=196)

Group	Ejection Fraction (%)	HbA1c = 7% n = 35 n (%)	HbA1c > 7% n = 161 n (%)	p-value
1	< 30%	2 (5.71%)	12 (7.45%)	0.02
2	30-44%	5 (14.28%)	52 (32.29%)	<0.00
3	45-54%	11 (31.42%)	79 (49.06%)	<0.00
4	= 55%	17 (48.57%)	18 (11.18%)	<0.00

Figure 1 and 2 shows that there was weak positive correlation between HbA1c and plasma BNP levels in optimal control group (r = 0.3, p = 0.92) and positive, weak but significant correlation between HbA1c and plasma BNP levels in suboptimal control group is (r = 0.2, p = 0.01).Also there was negative but significant correlation between HbA1c and EF in both groups as shown in Figure 3 and 4 (optimal control group: r=-0.3, p=<0.00; sub-optimal control group: r = -0.4, p = 0.01).

Figure 1: Correlation between HbA1cand BNP Levels in Optimal Control Group

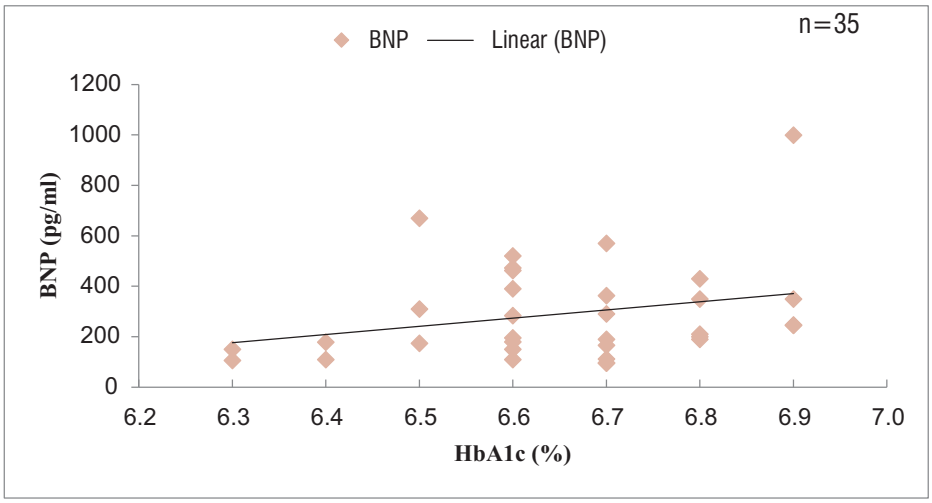


Figure 2: Correlation between HbA1cand BNP Levels in Suboptimal Control Group

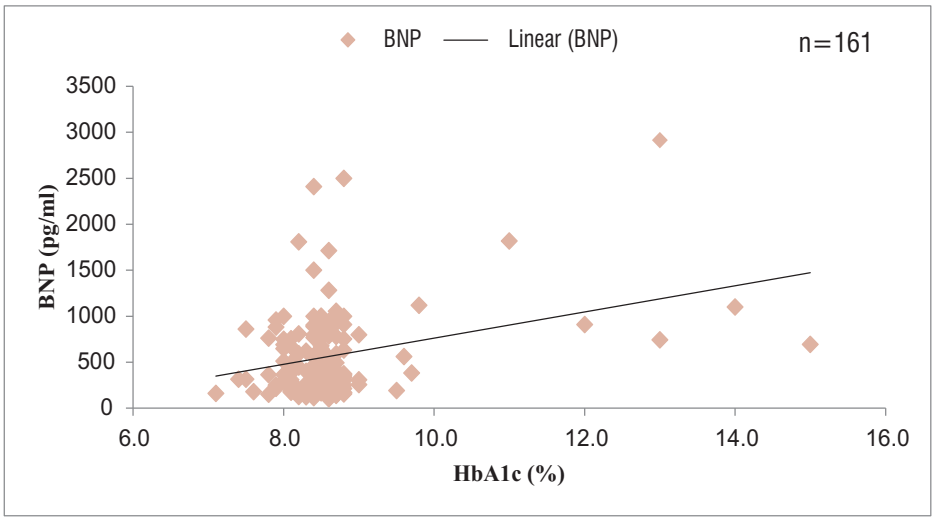


Figure 3: Correlation between HbA1cand Ejection Fraction (EF) in Optimal Control Group

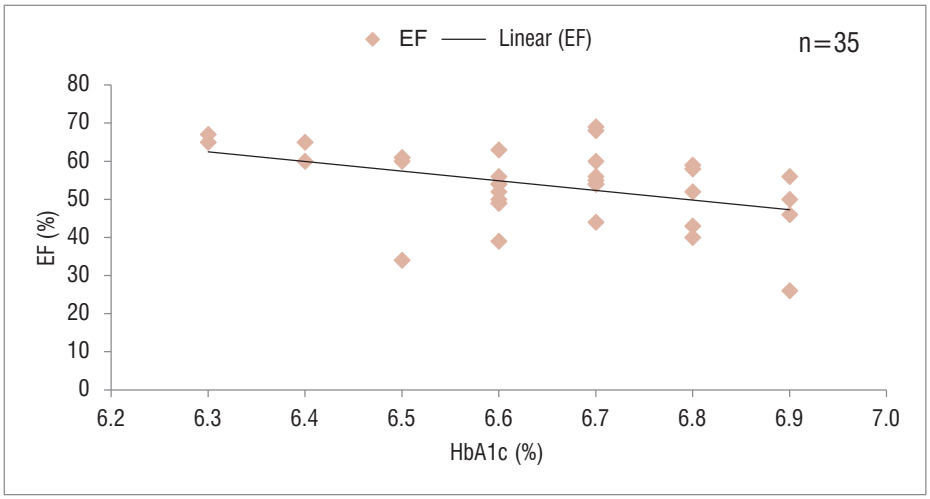
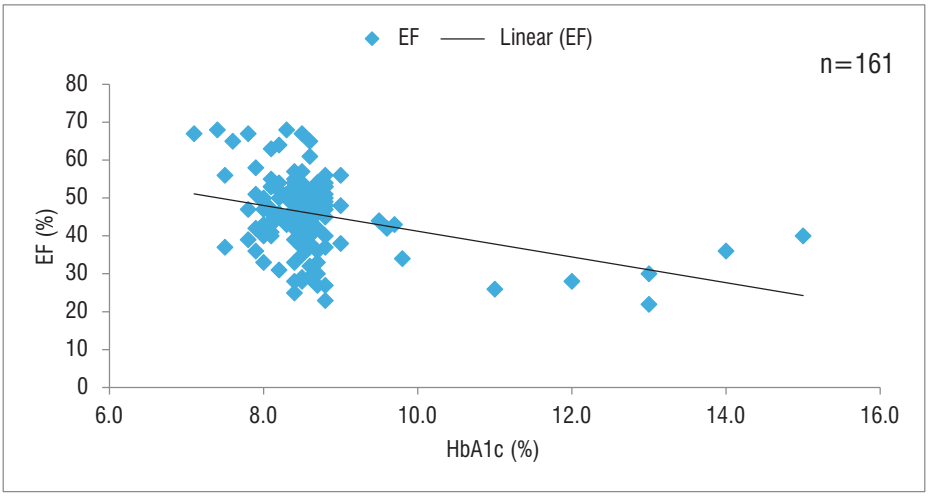


Figure 4: Correlation between HbA1c and Ejection Fraction (EF) in Suboptimal Control Group



DISCUSSION

In the present work, 17.86% patients had optimal HbA1c levels (⩽ 7%) as compared to 82.14% patients who had suboptimal HbA1c levels (> 7%). The mean HbA1c level of optimal control group was 6.67±0.18 % which is higher than the mean of HbA1c level of suboptimal control group which was 8.65±0.98 % (Table 1). These findings are in agreement with several previous studies of Corpus et al.; Chan et al., and Kassaian et al., with significant difference between groups.[15-17] Narayana et al., have reported that in the patients of concurrent DM and AMI, difference of 1% HbA1c increases the risk of subsequent mortality by 18-20%.[18] This may be an alarming fact that in the current work undertaken, there is a difference of almost 2% between study groups which suggests that subjects in suboptimal control group are at higher risk of subsequent mortality.

Another important observation is that there is significant relationship between glycemic control and LV functions in post-AMI diabetic patients (Table 1). The Ejection Fraction (EF) of those diabetic patients who had better glycemic control was better than those who had poor glycemic control. In addition to EF, there was also significant difference ($p = <0.05$) in the fractional shortening and LVESd between two groups. Aguilar et al., also found the similar results of strong association between preserved LV functions and lower quintiles of HbA1c.[19] However, this finding of significant association between optimal diabetic control and short-term outcomes is in conflict with the results of Kassaian et al.[17] Their study showed that there was insignificant difference between two groups in those diabetic AMI patients who have ejection fraction less than 30% ($p = 0.21$). Similarly, there was no such significant association in the conclusion of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS).[20,21] This is probably due to the difference in the study design as DCCT and UKPDS were cohort studies (patients were assessed at multiple points in time before final conclusion was made) whereas this research has cross-sectional study design in which blood samples were collected in the acute phase of AMI. Also, the sample size of above mentioned studies was quiet large in comparison to the current study.

Association between glycemic control and echocardiographic parameters was also analyzed and significant linear correlation was found. This outcome is consistent with the recently done study of Ashraf et al.,.[22] However, the strength of correlation in the current work ranges from moderate to weak (Figure 1, 2, 3 and 4). This might be due to the recording of echocardiographic parameters in the acute phase of AMI in this study. Nalbantic et al., have reported that myocardial changes sometime become apparent in subacute phase after ischemia.[23]

Minicucci et al., have indicated that approximately 25% patients of post-AMI patients develop heart failure.[24] Post-MI heart failure was assessed in this work biochemically by measuring plasma BNP levels. BNP was discovered by de Bold in 1988.[23] Hsich et al., have proved that levels of plasma BNP elevates in patients with heart failure.[25] Nalbantic et al., showed that plasma BNP level surges after AMI and is a reliable biochemical marker for quick and easy determination of LV functions in addition to echocardiography.[23] When heart failure was assessed by measuring plasma BNP levels in post-AMI diabetic patients, there was significant association between HbA1c and post-AMI plasma BNP levels. Plasma BNP levels of optimal glycemic control group was considerably lower than suboptimal control group (351.8±419.46 pg/ml vs 567.2±444.35 pg/ml, $p = 0.01$) as shown in Table 1.

LIMITATIONS

There are few probable limitations that need to be addressed. Firstly, the cross-sectional study design and non-randomized nature of sampling technique constitutes the major limitation of this study. In addition, blood samples were collected and echocardiographic data was recorded during the acute phase i.e., within 24 hours of admission. Whether left ventricular outcomes would have differed from the results of this study had another day been selected remains speculative.

CONCLUSION

The present work suggest that there is significant association between optimal glycemic control to achieve HbA1c levels $\leqslant$ 7% with a better LV systolic functions in diabetic patients admitted with AMI. It also highlights the importance of BNP in post-MI patients.

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