JRMI
Journal of Rehman Medical Institute

Volume 4, No. 3
July - September 2018
www.jrmi.pk

ORIGINAL ARTICLE

Can BNP levels and Killip grading assess the severity of injury to myocardium after acute myocardial infarction in Type II Diabetics?

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Submitted
July 19, 2018
Accepted
August 10, 2018

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Citation: Rehman S, Durrani M, Shah AA, Tariq K, Rehman AU, Shafiq M. Can BNP levels and Killip grading assess the severity of injury to myocardium after acute myocardial infraction in type II Diabetics? J Rehman Med Inst. 2018 Jul-Sep;4(3):3-7.

ABSTRACT

Introduction: Post myocardial infarction risk assessment and stratification is done clinically using Killip Scale as well as biochemically by measuring plasma B-type Natriuretic Peptide (BNP) levels.

Objective: To compare the validity of the two diagnostic modalities in type II diabetic patients who had recently suffered from acute myocardial infarction (AMI).

Materials & Methods: This descriptive cross-sectional study was conducted on 196 type II diabetic patients admitted after first episode of AMI in the Department of Cardiology at Rehman Medical Institute (RMI) and Lady Reading Hospital (LRH) Peshawar from 1st November 2014 to 30th June 2015 through convenience sampling. The subjects were divided into two groups; optimal control group and sub-optimal control group on the basis of HbA1c levels. Blood samples were taken and analyzed for HbA1c and BNP levels. Killip scale grading and echocardiography were recorded. Post MI risk assessment was done by Killip scale as well as by plasma BNP levels. SPSS version 16.0 was used to analyze the data for descriptive and comparative statistics, keeping $p \leq 0.05$ significant.

Results: Significant difference ($p<0.001$) in the BNP levels were observed between optimal and suboptimal control groups with severe heart disease who had plasma BNP level of more than 900 pg/ml (5.71% vs 17.39%). No association was found between glycemic control and Killip scale grading ($p>0.05$). There was also no significant difference in classes (II, III and IV based on Killip scale grading) between two groups.

Conclusion: High BNP levels were recorded in post MI patients in both the groups whereas the Killip Scale grades did not differ significantly in BNP levels in post MI patients.

Keywords: Myocardial Infarction; Diabetes Mellitus Type 2; Natriuretic Peptide, Brain; Glycated Hemoglobin A.

The authors declared no conflict of interest. All authors contributed substantially to the planning of research, data collection, data analysis, and write-up of the article, and agreed to be accountable for all aspects of the work.

INTRODUCTION

Acute myocardial infarction (AMI), also known as heart attack is the most common among cardiovascular diseases (CVD). AMI is defined pathologically as "death of myocardial cells in addition to features indicative of cardiac ischemia".[1,2] 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.[3] In the United States, 1.5 million men suffer from AMI every year.[4] Of these, 71.4% are those who suffer AMI for first time and 28.6% are those who had one or more episodes of AMI in their life. In Pakistan, 5.09 million people suffer from AMI per year.[5] Approximately 300 different risk factors of myocardial infarction have been identified by various studies;[6] most notable are from the Framingham study, the MONICA (multinational monitoring of trends and determinants in cardiovascular disease) project, and the INTERHEART study such as age, male gender, genetic factors, active and passive smoking of tobacco, dyslipidemia, diabetes mellitus and hypertension.

Many epidemiological surveys indicate that approximately 25% patients of AMI develop heart failure.[7] The probability of developing heart failure and mortality after AMI in diabetics is 2 to 4 fold higher than those without diabetes due to decreased tolerance of myocardium to ischemic injury in diabetics.[8,9] The level of post-MI heart failure is graded according to the Killip scale as class I (having no clinical feature of heart failure), class II (having S3 heart sound, rales or crackles in <1/2 of lungs and elevated jugular venous pressure), class III (having acute pulmonary edema) and class IV {having cardiogenic shock (systolic blood pressure <90mmHg) or features of hypo-perfusion (oliguria, sweating and cyanosis).[10]

B-type natriuretic peptide (BNP) is a neurohormone, made up of 32 amino acids. It is released as pre-pro-BNP (134 amino acids) from myocardial wall in response to stress (pressure or volume overload). After AMI, the plasma BNP level increases rapidly for the first 24 hours due to

ischemia and necrosis of myocardium and then tends to stabilize.[10] Plasma BNP level, therefore, is considered as an important biochemical marker in the diagnosis, grading and management of heart failure patient. However, increased concentration after AMI reflects left ventricular (LV) dysfunction, LV remodeling, heart failure and poor prognosis; whereas low level is predictive of preserved LV function and good prognosis.[11,12] Its measurement also helps in risk assessment of CVD.[13]

Diabetes mellitus is a non-communicable progressive disease; characterized by hyperglycemia due to deficiency of insulin synthesis or diminished effectiveness. Diabetes mellitus has two major types: Type 1 diabetes mellitus also known as insulin-dependent diabetes mellitus and Type 2 diabetes mellitus (T2DM) also known as non-insulin dependent diabetes mellitus; which is about 90% to 95 % of all the diabetics.[14] Diabetes is an established and independent risk factor for myocardial infarction and it magnifies the risk of AMI about 5-fold.[9] It is also estimated that 80% of the deaths among diabetic patients are due to cardiovascular diseases.[15] The magnitude of effect of diabetes varies with 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.[16,17] The influence of optimal glycemic control (HbA1c ≤ 7%) on the LV functions in diabetics presenting with AMI has also not been clearly defined so far.[18]

Therefore, in this study post-MI risk assessment and stratification was done clinically using Killip Scale as well as biochemically by measuring plasma BNP levels in type II diabetics. The association between glycemic control and short term out comes (LV functions) was also investigated in these subjects who had first episode of AMI.

MATERIALS & METHODS

For this cross-sectional study conducted over seven months (1st November 2014 to 30th June 2015) at the Department of Cardiology, Lady Reading Hospital (LRH), Peshawar, and Cardiology Department of Rehman Medical Institute (RMI), Peshawar, ethical approval was obtained from Khyber Medical University (KMU) Ethics Board. Patients with type 2 diabetes who presented with first AMI and had received thrombolytic treatment within 12 hours of onset of chest pain were enrolled in the study. Non-probability (non-random) convenience sampling was used to select subjects. Sample size of 196 was calculated using WHO formula. Informed written consent was taken from the study participants. The subjects were divided into two groups; optimal control group and sub-optimal control group on the basis of HbA1c levels.

Data were collected on predesigned structured Performa. Patients' demographic data, past medical history including risk factors and co-morbidities of diabetes mellitus, clinical examination and Killip Scale grading were included as major variables. Clinical assessment of all patients was done and blood samples were taken and analyzed for random blood sugar (RBS), glycosylated hemoglobin (HbA1c) and BNP levels. Results of biochemical tests and echocardiogram findings of the patients were recorded.

Transthoracic echocardiography was done on all subjects included in the study by qualified sonographer and the values of LVEDd, LVESd, FS and EF were noted. Reference ranges of these variables are: LVEDd = 36-56 mm, LVESd = 20-41 mm, FS = 25-50% and EF ≥ 55 %.

Blood samples were analyzed in laboratory of RMI, Peshawar and the Peshawar Lab, Peshawar.

Glycosylated hemoglobin was quantitatively determined on Microlab 300 using Glycohemoglobin HbA1 Human kit from Roche Diagnostics.

BNP assay was performed on automated chemistry and immunology analyzer ARCHITECT plus ci8200 using ARCHITECT BNP Kits from Abbott Diagnostics

All data of different variables were entered into the computer on regular basis and processed by using SPSS version 16. Mean and standard deviation were calculated for expressing continuous variables; for categorical variables, frequency and percentage were calculated. Data of the groups were compared using Chi-square test for categorical variables and student's T-test for continuous variables. Correlation was done using Pearson's *r* for nominal data. In the study, level of significance was set at $p \leq 0.05$ for all statistical analysis.

RESULTS

A total of 196 diabetic subjects from both sexes were included in the work undertaken. For the purpose of analysis, subjects were dichotomized on the basis of levels of HbA1c; HbA1c ≤ 7% was taken as good glycemic control (the optimal control group) and HbA1c > 7% was taken as poor glycemic control (the suboptimal control group). Furthermore, the analysis was done without separating subjects into groups.

Table 1 shows that out of 196 patients, 35(17.86%) patients had HbA1c ≤7% (optimal control group) having mean HbA1c of 6.67±0.18 (CV=0.03) and 161 (82.14%) patients had HbA1c >7% (suboptimal control group) having mean HbA1c of 8.65±0.98 (CV= 0.11), showing a significant difference between these two groups (p<0.001).

Table 1: Study groups based on HbA1c levels (n=196).

Groups	Number of Patients (n)	Percentage (%)	Mean ± SD of HbA1c	Coefficient of Variation (CV)	p-value
Optimal control group (HbA1c ≤ 7)	35	17.86	6.67±0.18	0.03	<0.001
Suboptimal control group (HbA1c > 7)	161	82.14	8.65±0.98	0.11	

In optimal control group (HbA1c ≤7, n=35), 15 (42.9%) patients had heart failure while 20 (57.1 %) patients didn't develop heart failure. In this group, eight (22.9%) patients were in Killip Class II, four (11.4%) were in Killip Class III, and three (8.5%) were in Killip Class IV. In suboptimal control group (HbA1c >7, (n=161), 69 (42.9%) patients had heart failure while 92 (57.1%) patients did not develop heart failure. In this group, 22 (13.7%) patients were in Killip Class II, 32 (19.9%) were in Killip Class III, and 15 (9.3%) were in Killip class IV (Table 2).

Table 2: Killip Scale distribution of the study groups based on HbA1c levels (n=196).

#	Killip Class	HbA1c ≤ 7% n (%)	HbA1c > 7% n (%)	p-value
1.	I	20 (57.1)	92 (57.1)	1.00
2.	II	8 (22.9)	22(13.7)	0.28
3.	III	4 (11.4)	32 (19.9)	0.34
4.	IV	3 (8.5)	15 (9.3)	0.90
Total n (%)		**35 (17.86)**	**161 (82.14)**	

Out of 196 subjects, only two patients belonging to the optimal control group had no stress on heart (BNP level ≤100 pg/ml). While 57.1% had some stress on heart (BNP level = 101-300 pg/ml) in suboptimal control group as compared to 31.68% in optimal control group (p = 0.03), 28.57% had mild stress (BNP level = 301-600 pg/ml) in suboptimal control group as compared to 31.05% in optimal control group (p = 0.01). Only one (2.85%) subject had moderate heart stress (BNP level = 601-900 pg/ml) as compared to 32 (19.87%) subjects in optimal and suboptimal control group respectively (p<0.001). There was similar significant difference (p<0.001) between optimal and suboptimal control groups with severe heart disease who had plasma BNP level of more than 900 pg/ml (5.71% vs 17.39%) as shown in (Table 3).

Table 3: Level of Stress on Heart of the Study Groups Based on HbA1c Levels (n=196).

#	BNP Levels (pg/ml)	Level of Stress on Heart	HbA1c ≤ 7% n = 35	HbA1c > 7% n = 161	p-value
1.	< 100	No stress on heart	2 (5.71)	0 (0)	N/A
2.	101-300	Some stress on heart is present	20 (57.1)	51 (31.68)	0.03
3.	301-600	Mild stress on heart is present	10 (28.57)	50 (31.05)	0.01
4.	601-900	Moderate stress on heart is present	1 (2.85)	32 (19.87)	<0.001
5.	> 900	Severe stress on heart is present	2 (5.71)	28 (17.39)	<0.001
Total n (%)			**35 (17.86)**	**161 (82.14)**	

Figure 1 shows the scatterplot of correlation between HbA1c and BNP levels of the suboptimal control group subjects. A positive, though weak correlation is plotted which is significant (r=0.2, p=0.01).

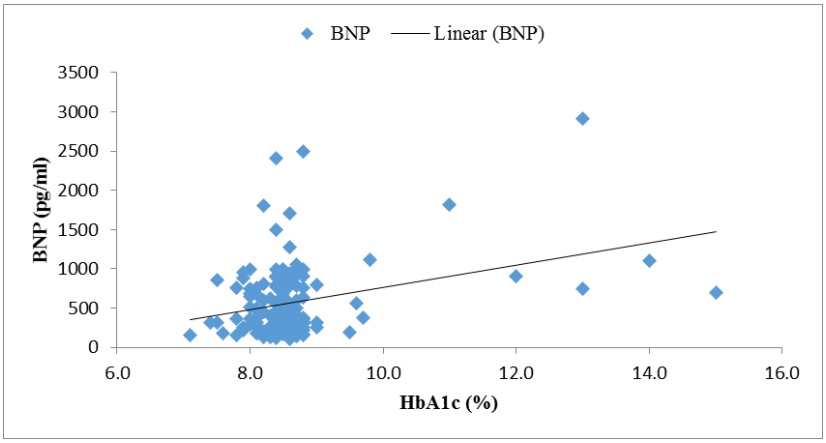

Figure 1: Scatterplot showing positive, weak but significant correlation between HbA1c and plasma BNP levels in suboptimal control group, (r=0.2, p=0.01).

DISCUSSION

Diabetes Mellitus (DM) is a well-known risk factor for cardiovascular diseases. The patients of T2DM have high risk of AMI than non-diabetic individuals.[19] The association of short-term outcome with glycemic control in T2DM patients who had a recent attack of AMI were evaluated in this study. There was significant association between good glycemic control and improved short-term outcomes. The diagnosis of AMI was based on guidelines presented by third Global MI Task Forces.[1,20,21] The short-term outcomes were measured by recording the echocardiographic findings (LVEDd, LVESd, fractional

shortening and ejection fraction) and measuring plasma BNP levels.

The mean HbA1c of 196 subjects was 8.28 ± 1.16%. The mean HbA1c level of optimal control group was higher than the mean of HbA1c level of suboptimal control group (Table 1). These findings are in agreement with several previous studies,[22-24] with significant difference between the two groups. Narayana et al (2015)[24] have reported that in the patients of concurrent DM and AMI, difference of one percent HbA1c increases the risk of subsequent mortality by 18-20%. This is 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. Minicucci et al (2011)[7] have indicated that approximately 25% patients of post-AMI patients develop heart failure. Post-MI heart failure was assessed in this research biochemically by measuring plasma BNP levels and clinically by using Killip Scale criteria. Killip scale was also used to stratify subjects into Killip Class I, II, III and IV according to clinical assessment.

B-type natriuretic peptide is released from myocardial wall and its plasma level has relevance with heart failure. Hsich et al (2013)[25] have proved that levels of plasma BNP elevates in patients with heart failure. Duran-Nalbantic et al (2012)[26] 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. When heart failure was assessed by measuring plasma BNP level in post-AMI diabetic patients, there was significant association between HbA1c and post-AMI plasma BNP level. Plasma BNP level of optimal glycemic control group was considerably lower than suboptimal control group (p=0.01).

When heart failure frequency was determined by Killip Scale grading criteria, present study revealed that 57.14% subjects did not develop heart failure whereas 42.86% subjects were in heart failure (Table 3.2). Similar results were obtained by Khan et al (2011)[27] in which 39.5 % diabetic patients developed heart failure after AMI and both the studies have comparable sample size (182 in Khan et al, 2011 and 196 in this study). These findings are slightly different than the results of another study of Khan et al (2012)[28] in which 63% post-AMI patients did not developed heart failure, and 37% develop heart failure. Among those who developed heart failure, 15.31% were in Killip Class II, 18.37% were in Killip Class III and 9.18% were in Killip Class IV (Table 3.2). Mak et al (1997)[29] showed that only 1-2% subjects were in Killip Class IV.

In the present study, no association was found between glycemic control and Killip scale grading (p = >0.05). There was also no significant difference in classes (II, III and IV) between two groups (Table 3.10). Although both Killip Scale and plasma BNP levels were used to assess heart failure but there results in terms of association with HbA1c came out to be indifferent with each other contrary to expectations. This conflict might be due to difference in the interpretation of clinical assessment of sign and symptoms and other features of Killip Scale grading by different examining individuals. Another reason could be the timing of blood sample taken during the acute phase of AMI for plasma BNP measurement. Various studies[30,31] have reported that after AMI, BNP level peaks twice. The first wave of plasma BNP level peaks after 16 hours of myocardial infarction followed by second wave which peaks on day three or day four. This phenomenon may yield data where interpretation becomes difficult and inconclusive. Therefore, it is suggested that further studies be carried out to follow the BNP levels during the peaks after AMI and their relationship is ascertained with Killip grading and glycemic control.

CONCLUSION

Plasma BNP levels and Killip Scale grading alone cannot predict the severity of myocardial injury. Clinical evaluation by a clinician is also worth considering while estimating the myocardial insult.

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