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Medicine

COMPARISON ON VALUES OF MMP-2 AND PRO-BNP TO IDENTIFY THE RISK OF ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Introduction: The present study has been planned to assess the levels of MMP-2 and Pro-BNP in patients suffering with Diabetes mellitus. the study showed that levels of above said inflammatory biomarkers at different time intervals and it was first to report the levels of biomarkers in AMI patients with DM.

Material And Methods: 86 patients were selected and divided into two groups, Group A included 43 healthy volunteers, Group B included patients with DM and suffering from AMI. Blood concentration of biochemical parameters related to AMI was assessed at the baseline and levels of MMP-2 and Pro-BNP were assessed via ELISA kits at 0th , 30th ,60th and 90th day of the enrolment of DM patients with AMI.

Results: Assessment of biochemical parameters were done and found significantly increased levels was found in group B as compared to group A. Among the DM patients with AMI (confirmed as per guidelines) in group B, MMP-2 and Pro-BNP levels were found significantly decreased on 0th day to 30th day (P=5.28E-16 and P=1.5E-22), 30th day to 60th day (P=1.04E-07and P=1.2E-30)and 60th day to 90th day (P=5.37E-05 and P=1.66E-12) respectively. Plasma levels of Pro-BNP and MMP-2 were correlated and Pro-BNP levels were still found significantly increased on the 90th day of enrolment of DM patients.

Discussion Time dependent relationships were found in Pro-BNP and MMP-2 serum levels, therefore these biomarkers were directly correlated with AMI. At 90th day, Pro-BNP levels were found significantly increased as compared to healthy volunteers of group A.

KEYWORDS : Acute myocardial infarction, MMP-2, Pro-BNP, Diabetes mellitus

INTRODUCTION -

Acute myocardial infarction is the most common etiology of chronic heart failure (CHF)(Pratesi et al 2016) and as per recent criteria on the diagnosis of acute myocardial infarction (AMI), presence of typical symptoms, development of Q-waves in ECG, serum levels of CKMB (>10 ng L) and serum troponin (T>0.05 ng/ mL) should be analysed (Zimetbaum et al 2003 and Mullins KE et al 2020). It has also been noted that AMI is the best indicator to find the prognosis and development of CHF. Disruptive changes in the extra cellular matrix is the major consequences of AMI (Cahill TJ et al 2017). However, The structural and functional integrity of myocardium was maintained by extracellular matrix. During extracellular matrix degradation matrix metalloproteases i.e. gelatin proteases plays a crucial role. Infact, matrix metalloproteinases is responsible to maintain the vesicle integrity and helpful in the formation of extra cellular matrix (Ushakov A et al 2020) . These gelatinases are found to be elevated in the blood in acute myocardial infarction which is the major cause of death and disability worldwide (Jones CB et al 2003). It has been also found that ventricular remodelling is associated with levels of matrix metalloproteinases 2 and 9 (Kai H et al 1998).

Studies suggest that MMP-2 and NT Pro BNP(biologically inert and 17 peptide ring structure) has long term remodeling effect after complicated myocardial infarction whereas this natriuretic peptide synthesis occurs in both infarcted and non-infarcted myocardium Olsson LG et al 2007 and Omland et al 2002). NT Pro BNP has a very crucial role in the examination of patients suffering with syncope and the levels of NT Pro BNP is drastically increased in the patients diagnosed with heart failure, cardiac arrhythmia and in cardiac syncope. It is a best indicator that could have a very good role introduction of patients with syncope (Pfister et al 2012).

We therefore assessed NT-pro-BNP and MMP-2 in diabetic patients hospitalized for acute myocardial infarction to our cardiological department and compare the diagnostic and prognostic levels of MMP- 2 anti Pro BNP in the patients suffering with diabetes mellitus during a 3- months follow-up.

MATERIALAND METHOD:-

The study was a prospective observational study on diabetic patients with a risk of acute myocardial. In this study, correlation of inflammatory marker and NT pro BNP was assessed to know the risk of acute myocardium in diabetic mellitus patients. With this purpose, the study was conducted from1st Jan 2021 to 30th July 2021 in Rajshree Medical Research Institute Bareilly, Uttar Pradesh India and approved by the local ethical review committee with letter no RMRI/IEC/2020/ 0014 on dated 01/12/2020.

Population Under Study:-

86 participants were selected from Rajshree Medical Research Institute Bareilly, Uttar Pradesh India. Only those participants were included who fulfilled the criteria. Guidelines produced by joint European society of cardiology and American college of cardiology committee for myocardial infraction were used for diagnosing AMI (consensus document and He Wm et al 2016). For the enrolment of patients in the study, CKMB, Troponin T levels and changes found in ECG were assessed by faculty members of department of Medicine Rajshree medical research institute Bareilly UP, India as per the guidelines (Jernberg T el al 2000).

Patients were called for an ambulance with chest discomfort and symptoms related to acute myocardial infraction. Inclusive criteria include dyspnoea without asthma or any other lung disease, with diabetes mellitus without hypertension and chest pain with unknown reason. Patients having DM suffering with chest pain were pre diagnosed with prehospital ECG in ambulance via well trained nurses. For the above purpose, four well equipped ambulances were used. The evaluation of selected markers were assessed on first day of enrolment and every 30th day of the starting of the treatment and followed up to 3 months.

In the exclusive criteria, patients with a history of smoking, alcohol consumption, were excluded. The participants having inadequate response to the classical treatment for AMI were ineligible for assessment of biochemical markers. The participants who were noticed with are toxicity and adverse effect of the drugs were excluded from the study.

Study population of 86 patients were divided in two groups. Group A includes forty three healthy voluntary persons and Group B includes forty three DM patients on classical treatment for AMI out of 50 patients (as per exclusive criteria 2 patients with hypertension, 2 patients with angina pectoris and 3 patients with myocardial infarction were rejected). Group B participants were followed up for 3 months

and are asked to visit the hospital on every 30th days to 90th day. The vital parameters like blood pressure, pulse and any adverse reaction from the selected drugs were keenly observed by trained nurses. Biochemical markers related to the study were assessed after every 30th day, 60th day and 90th day from the enrolment of the patients.

Estimation Of Various Parameters:-

In blood concentration of Hb, Albumin, D- Dimer, total cholesterol, triglyceride, total bilirubin, alanine transaminase, aspartate transaminase, Uric acid, C- reactive protein and CK-MB were assessed by kit methods and estimation was done by trained technician under supervision of doctors. Standard procedures for estimation were used as per instructions mentioned on kit.

NT-pro BNP (Pfister R et al 2009) and MMP -2 (Squire IB et al 2004) were measured in triplicates by the expert technicians and under the observation of the faculty members of central laboratory of Rajshree medical research institute Bareilly . Serum from the group B patients were collected for analysis at first day, 30th day, 60th day and 90th day of treatment. ELISA (Enzyme linked immunosorbent assay) kits for NT-pro BNP and MMP -2 were purchased from R & D systems (Minneapolis, MN USA). CRP levels will be measured by kit from Indianapolis, IN, USA).

Statistics

For the assessment of this study, SPSS-16 version 16.0 Inc., Chicago USA was used. The comparison between the group A and B were assessed. *P* values below 0.05 was considered statistically significant. The measurement data conforming to the normal distribution were expressed as (mean ± SD), and t-test/z-test was performed for the comparisons between groups.

Table 1- Comparison Of The Base Line Patients Characteristics (n= 86) Among The Groups At The Time Of Enrolment

S. No.			Group A (43 healthy volunteers)	Group B (43 patients with DM)	P value
1	Age		45±12	47±07	
2	Sex Male/Female (percentage		58/42	62/38	
3	Heart rate at admission		72±12	87±23	
4	Previous history	MI	NA	03*	
		Angina pectoris	NA	02*	
		Hypertension	NA	02*	
		Diabetes mellitus	NA	43	
5	Blood pressure (mm/Hg)	Systolic	120±26	147±56	
		Diastolic	67±34	80±34	
6	Hb (g/L)		16.2±1.1	15.9±1.2	
7	Alb (g/L)		6.8±1.5	5.9±1.6	
8	D- dimer (µg/L)		436±112	756±453	0.001
9	Total cholesterol (mmol/L)		3.31±1.23	4.86±2.65	0.001
10	Triglyceride (mmol/L)		1.45±0.32	1.97±0.86	
11	Total bilirubin (µmol/L)		1.96±0.65	2.65±0.98	
12	ALT (U/L)		46.23±12.82	90.21±21.22	0.001
13	AST (U/L)		32.89±15.35	145.44±24.76	0.001
14	UA (µmol/L)		5.21±2.11	8.22±2.89	
15	CRP (mg/L)		14.33±4.15	97.34±37.11	0.001
16	Hospital stay (days)		NA	11±5	
17	NT-pro BNP (pg/mL)		3981.85± 832.79	12679.30± 4566.93	0.53
18	CK-MB		2.22±1.12	134.65±89.22	0.001
19	Highest MMP-2 (ng/mL)		423.80± 103.90	1317.83± 507.01	0.58
20	Creatinine		0.92±0.13	1.12±0.54	

Value were shown here in Mean ± SD

Note = * patients having signs of myocardial infarction, angina pectoris and hypertension were excluded from the study.

P values were calculated via Wilcoxon rank sum test for comparison among group A and group B.

Table 2 - Comparison Of The Serum Concentration Of Metalloproteinases -2 (ng/mL) Between The Groups At Three months Follow Up

	Levels of metalloproteinases -2 (ng/mL)				
S. No.		**1st day**	**30th day**	**60th day**	**90th day**
1	Group A	423.80± 103.90	------	------	------
2	Group B	1317.83± 507.01	1272.42± 458.93	1039.66± 310.98	475.30±96. 05
	P values	0.58*	0.78**	0.76***	0.28****
			5.28E-16#	0.00017##	0.01108###
				1.04E-07$	0.00205$$
					5.37E-05a

Note – *P* values were calculated via Wilcoxon rank sum test for comparison among group A and group B.
the values were shown here in Mean ± SD

* *P* value were obtained after comparison of group A and group B at baseline
***P* value were obtained after comparison of group A and group B at 30th day
***P* value were obtained after comparison of group A and group B at 60th day
**** *P* value were obtained after comparison of group A and group B at 90th day
#*P* value were obtained after comparison of group B at the time of enrolment and group B at 30th day
P value were obtained after comparison of group B at the time of enrolment and group B at 60th day
P value were obtained after comparison of group B at the time of enrolment and group B at 90th day
$. *P* value were obtained after comparison of group B at 30th day and group B at 60th day
$$. *P* value were obtained after comparison of group B at 30th day and group B at 90th day a *P* value were obtained after comparison of group B at 60th day and group B at 90th day.

Table 4 - Comparison Of The Serum Concentration Of NT-pro BNP (pg/mL) Between The Groups At Three Month Follow Up

	Levels of NT-pro BNP (pg/mL)				
S. No.		**1st day**	**30th day**	**60th day**	**90th day**
1	Group A	3981.85±832.79	-------	-------	-------
2	Group B	12679.30±456 6.93	10677.88 ±3597.93	9042.85± 3045.60	6091.23± 2640.64
	P values	0.53*	0.31**	0.26***	0.12****
			1.5E-22#	8.4E-18##	1.06E-07###
				1.2E-30$	1.17E-10$$
					1.66E-12a

Note *P* values were calculated via Wilcoxon rank sum test for comparison among group A and group B.
Value were shown here in Mean ± SD

**P* value were obtained after comparison of group A and group B at baseline
***P* value were obtained after comparison of group A and group B at 30th day
***P* value were obtained after comparison of group A and group B at 60th day
****P* value were obtained after comparison of group A and group B at 90th day
#*P* value were obtained after comparison of group B at the time of enrolment and group B at 30th day
P value were obtained after comparison of group B at the time of enrolment and group B at 60th day
P value were obtained after comparison of group B at the time of enrolment and group B at 90th day
$ *P* value were obtained after comparison of group B at 30th day and group B at 60th day
$$ *P* value were obtained after comparison of group B at 30th day and group B at 90th day
a *P* value were obtained after comparison of group B at 60th day and group B at 90th day

RESULTS

The plan of the study was to assess the levels of MMP-2 and NT-pro

BNP in the participants with diabetes mellitus suffering with AMI. The concentrations of MMP-2 and NT-pro BNP were assessed at the time at the time enrolment, 30th day, 60th day and 90th day of DM patients with symptoms of AMI(after conformation as per the guidelines). The demographic profile of selected patients were presented in the table-1.

At the baseline characteristic, no significant difference was seen in the demographic profile within the group A (consist of 43 healthy volunteers). Primary diagnosis of AMI were done by watching the dynamic changes in ECG (ST- segment ort Wave changes) and biochemical parameters required for diagnosis of AMI were assessed at the baseline (Group B). In total, 86 patients were recruited.

Levels Of Biomarkers In DM Patients Of Group B With Confirmed AMI:-

In table 1, group A (58% men) and group B (62% men)participants has mean age of 45±12 years and 47±07 respectively. Group B DM patients has significantly elevated plasma concentrations of D-dimer, total cholesterol, triglyceride, total bilirubin, ALT, AST,UA, CRP and CK MB than group A healthy volunteers.

Levels Of Metalloproteinases -2:-

Serum MMP-2 levels were assessed in group A and B, it was found that normal levels of healthy individuals was 423.80±103.90 ng/ml. It was observed that in group B baseline levels of MMP -2 was found 1317.83±507.01 ng/ml and concentrations of MMP-2 were constantly decreases as the levels were assessed after every 30th day up to 90th day of enrolment. Hence, there was a significant decrease in the levels of MMP-2 in patients on 0th day to 30th day (P=5.28E-16), 30th day to 60th day (P=1.04E-07)and 60th day to 90th day (P=5.37E-05)of enrolment(as shown in table 3)

Levels of NT-pro BNP:-

Serum NT-pro BNP were assessed in group A and B, it was found that normal levels of healthy individuals was 3981.85±832.79 ng/ml. It was observed that in group B baseline levels of metalloproteinases were found 12679.30±4566.93 ng/ml and concentrations of NT-pro BNP were constantly decreases as the levels were assessed after every 30th day up to 90th day of enrolment. There was a significant decrease in the levels of NT-pro BNP in patients on 0th day to 30th day (P=1.5E-22), 30th day to 60th day (P=1.2E-30)and 60th day to 90th day (P=1.66E-12)of enrolment(as shown in table 4).

DISCUSSION

43 patients with DM has been selected to check the effectiveness and time dependent relationship of two biomarkers i.e. MMP-2 and NT-pro BNP. These markers has clinical significance for the assessing the prognosis of AMI (Nagaya et al 1999).

Reports on serum NT-pro BNP levels depends on age and race of patients, documented that NT-pro BNP levels increases as the age of individual increases (Whiteman IR et al 2019). These results are similar to our finding where age has direct relationship with NT-pro BNP levels. Moreover, the levels of NT-pro BNP was found high in the patients suffering with DM9 Fringu FT et al 2020). These result were found similar to finding observed by Talwar S et al 2000. Significantly high levels of NT-pro BNP is associate with congestive heart failure in elderly population.

Studies on the diagnosis of AMI showed that not only the relevant patient symptoms but also the deranged ECG is not useful criteria for selecting AMI participants (Docherty AB et al 2018). As per guidelines, biochemical markers will also assessed because of their association with high risk of death in AMI patients (Na 'slund U et al 2002). This is mandatory to increase the diagnostic accuracy of biochemical parameters in patients. In group B, the levels of CKMB, total cholesterol and CRP were increased that confirmed the AMI in relation to onset of symptoms.

In our study, among patients of group B 65% has an initial deranged ECG and 35% has increased CKMB(data not shown). Similarly MMP-2 levels were found at significantly high among the participant of group B at the 90th day of enrolment. These results were found similar to Wang W et al 2002). This significant increase was not much more pronounced as compare to levels of NT-pro BNP on 90th day of enrollment. This show that NT-pro BNP is cleared via different mechanism and has longer half life as compare to MMP-2 where researcher has reported that MMP 2 has inverse correlation with left ventricular volume (Nagaya et al 1999 and Ohtsuka et al 2003).

CONCLUSION

In conclusion, AMI survivors with i.e. diabetis mellitus will be at high risk and that may lead to worse outcome and levels of NT-pro BNP must be checked at regular intervals for assessing the severity of AMI.

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