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Clinical Utility of N-Terminal Prohormone B-Type Natriuretic Peptide Levels in Patients of Type 2 Diabetes Mellitus with Heart Failure

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ABSTRACT

Objective: To evaluate the effect of type 2 diabetes mellitus on plasma N-terminal prohormone B-type natriuretic peptide levels in patients with heart failure and correlate it with glycosylated haemoglobin levels.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Department of Chemical Pathology in collaboration with the Department of Cardiology, Combined Military Hospital, Multan Pakistan, from Feb to Sep 2021.

Methodology: We assayed plasma NT-pro BNP levels in 194 individuals with established heart failure, (98 non-diabetics, and 96 patients with diabetes). Plasma NT-pro BNP levels were compared between groups in addition, the correlation of glycosylated haemoglobin with plasma NT-pro BNP levels was explored.

Results: The mean plasma NT-pro BNP values were higher in patients with diabetes (15826.08 ± 8143.434pg/mL) than in non-diabetics (12534.06±6323.92pg/mL) with a *p*-value 0.02. When NT-pro BNP was compared there was no significant found difference between the non-diabetic group and the Controlled Diabetes-Group (*p*-value 0 .882), but it was significantly higher in the Uncontrolled Diabetes-Group (*p*-value<0.001). A moderate positive association was found between NT-pro BNP and glycosylated haemoglobin (r=0.541, *p*-value<0.001).

Conclusion: Although obesity has an inverse relation with plasma natriuretic peptides level and most patients with diabetes are overweight, the plasma NT-pro BNP is still a very informative tool and holds its significance as a diagnostic and prognosis marker in diabetic patients with heart failure.

Keywords: Body mass index, Diabetes mellitus, Heart failure, Natriuretic peptides.

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INTRODUCTION

Heart failure is the leading cause of morbidity and premature mortality worldwide. Early diagnosis and optimum management are crucial factors in reducing its impact. The clinical utility of B-type Natriuretic Peptide is well established in the diagnosis, monitoring and risk stratification of cardiovascular diseases (CVD).[1,2] The role of B-type Natriuretic Peptide (BNP) and/or N-terminal prohormone B-type natriuretic peptide (NT-proBNP) is highly emphasized in heart failure (HF), particularly with well-preserved ejection fraction (EF>50%).[3] BNP is a neurohormone exclusively expressed in the heart. It is a principal cardiac natriuretic peptide secreted mainly from the ventricles as a response to stretch in the myocardium stretch resulting from volume expansion, pressure overload and angiotensin II stimulation.[3,4]

Most of our clinical assays predominantly detect non-glycosylated pro-BNP.[5] It has been found that almost 80% of B-type natriuretic peptides present in the human circulation of HF patients have central glycosylation.[6] Multiple studies have established the relationship between glycosylation and lower detectable levels of NT-proBNP.[7,8] Thus, low BNP levels in obese are partially attributed to altered clearance receptors, peptide degradation and increased glycosylation with impaired enzymatic processing.[9] On the other hand, it has been found that fasting and weight loss reduce the expression of NP clearance receptors on adipocytes.[10] Several pieces of evidence and descriptions are proposed to elucidate the finding of better survival in HF patients with obesity.

Pathogenesis of T2DM is linked with insulin resistance and obesity. Most patients with T2DM are obese and also prone to develop HF. Diabetes and obesity are independent risk factors for cardiovascular diseases. Nevertheless, evidence has proposed that obese individuals have low levels of circulating BNP and a high proportion of overweight and/or obesity in patients with T2DM. Limited data is available to demonstrate the relationship of BNP with T2DM in the presence of HF. Therefore, the current study was planned to investigate the effect of T2DM on plasma

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NT-proBNP levels in patients with HF and to explore the relation between NT-proBNP and HbA1c levels.

METHODOLOGY

The comparative cross-sectional study was conducted at the department of Chemical pathology in collaboration with the Department of Cardiology, Combined Military Hospital, Multan Pakistan, from February to September 2021 after approval of the Institutional Ethical Review Board (ERC No. 11/2020 dated 20 Sep 2020). The sample size was calculated using prevalence of congestive cardiac failure of 2.8 million.[11] One hundred ninety-four patients with HF were recruited in our study by a convenient non-probability sampling technique.

Inclusion Criteria: We included patients with an already established heart failure (HF) diagnosis for at least three months, on medications and symptomatic with different classes of dyspnea as per the New York Heart Association classification. Patients with diabetes and non-diabetic patients with HF were enrolled.

Exclusion criteria: Patients with advanced renal failure (serum creatinine >200umol/L), recent acute coronary syndrome (within the last 2 months), recent cardiac bypass surgery and bronchopulmonary disease were excluded from this study.

All study participants were enrolled in this study after informed consent. Detailed demographic features and clinical information were collected during the study and Body Mass Index (BMI) was calculated from the height and weight of each participant. Per the World Health Organization (WHO) guidelines, the study participants were categorized into three groups based on their BMI. Normal weight or lean (BMI <25.0 kg/m^2), overweight (BMI 25.0 to 29.9kg/m^2), and obese (BMI ≥30.0kg/m^2).[12] The respective physicians diagnosed HF and DM per guidelines of the 2021 European Society of Cardiology (ESC) and 2019 American Diabetes Association (ADA) criteria respectively.[13]

Five millilitres of venous blood from all participants were collected into two separate Ethylenediamine tetra-acetic acid (EDTA) tubes (1mg/ml blood), one for plasma NT-proBNP and the other for Glycosylated haemoglobin (HbA1c). The NT-proBNP specimen was centrifuged at 3400rpm for three minutes to get the plasma. Plasma NT-proBNP levels (pg/mL) were analyzed on the same day of blood sample acquisition on a fully automated Chemiluminescence immunoassay analyzer Architect i1000SR by Abbott. Patient categorization was done based on NYHA functional class criteria for the severity of HF. Study participants were stratified into two groups based on the presence or absence of diabetes mellitus. The HbA1c of each participant was analyzed on the same EDTA sample using National Glycohemoglobin Standardization Program (NGSP) recommended method (capillary electrophoresis) on full autoanalyzer CAPILLARYS-3-TERA. The cut-off for diabetes was HbA1c≥ 6.5%, and FPG was≥7.0mmol/L (126mg/dL). Controlled or uncontrolled T2DM was established on the basis of HbA1c, HbA1c>7.0mmol was labelled as uncontrolled T2DM.[14]

Statistical analysis was carried out using Statistical Package of Social Sciences (SPSS) version 26:00 Mean±SD was calculated for continuous variable. In addition, frequency and percentage were calculated for categorical variables. Mean HbA1c, NT-proBNP, BMI and age between diabetes and non-diabetic patients were compared by using an independent sample T-test and ANOVA (Post hoc LSD) was used to compare NT-proBNP between controlled diabetes, uncontrolled diabetes and non-diabetics groups and different NYHA groups. Pearson's correlation was used to find a correlation between HbA1c and NT-proBNP.

RESULTS

Out of 194 patients with heart failure, 98(50.52%) were non-diabetics, and 96(49.48%) were already diagnosed with T2DM. The Diabetes-Group was further stratified based on HbA1c levels as controlled (HbA1c≤7.0%) and uncontrolled diabetes mellitus (HbA1c>7.0%). The mean HbA1c level of non-diabetics was 5.12±0.30%, and diabetes was 7.70±2.07%. Among people with diabetes, 38(39.6%) were uncontrolled diabetes with mean HBA1c of 9.74±1.90%, and 58 (60.41%) were controlled people with diabetes with HBA1c levels of 6.37±0.47% (Table-I).

Table-I: Comparisons Between Patients with Diabetes and Non-Diabetic Groups (n=194)

Parameters	Study Groups		*p*-value
	Diabetes Mellitus n=96 Mean±SD	Non-Diabetes n=98 Mean±SD	
Age years	59.28±14.43	62.35±14.79	0.146
HbA1c (%)	7.70±2.07	5.10±0.31	<0.001
BMI kg/m2	27.80±5.40	25.90±4.52	<0.001
NYHA Dyspnea Class	**n(%)**	**n(%)**	**-**
I	4(4.17%)	7(7.14%)	0.027
II	33(34.38%)	55(56.12%)	
III	37(38.54%)	28(28.57%)	
IV	19(19.79%)	11(11.22%)	

The mean NT-proBNP level for diabetes and non-diabetic groups were 15826.08±8143.434pg/mL and 12534.06±6323.921 pg/mL, respectively. There was a statistically significant difference between plasma NT-proBNP levels of the two groups (diabetes vs non-diabetics) p=0.02.

NT-proBNP levels were also compared by multiple comparisons of Post hoc LSD between different diabetic and NHYA groups. However, the levels were higher in uncontrolled diabetics than in non-diabetic and controlled diabetic patients (p-value <0.001). Similarly, NT-proBNP levels were highest in the NYHA-IV group than in all other groups (p-value <0.001), as shown in Table II.

Table II: Multiple Comparisons of NT-PRO BNP results in Different Groups

Groups	Mean Difference	Std. Error	p-value
No diabetes vs controlled diabetes	-161.709	1090.499	0.882
No diabetes vs uncontrolled diabetes	-8747.710*	1316.690	0.0001
Controlled diabetes vs uncontrolled diabetes	-8586.001*	1417.886	0.0001
NHYA1 vs NHYA2	-7647.648*	1705.328	0.0001
NHYA1 vs NHYA3	-14677.929*	1738.529	0.0001
NHYA1 vs NHYA4	-19431.303*	1879.590	0.0001
NHYA2 vs NHYA3	-7030.281*	872.119	0.0001
NHYA2 vs NHYA4	-11783.655*	1127.372	0.0001
NHYA3 vs NHYA4	-4753.374*	1176.989	0.0001

A moderate positive statistical correlation was found between NT-proBNP and HbA1c concentration in diabetic patients with HF (r=0.541, p-value<0.001). Moreover, we found that in patients with diabetes, there is a significant correlation between the degree of diabetic controls and NT-proBNP concentration. Heart failure patients with poor glycemic controls have higher NT-proBNP levels (21281.77±7507.881pg/ml) than their counterparts (12695.77±6762.598pg/ml). The degree of HF categorized based on clinical evaluation as per NYHA criteria was well correlated with plasma levels of NT-pro BNP both in diabetics and non-diabetics (Table-III). Pearson's correlation test showed a negative correlation between NT-proBNP and BMI (r=-0.301, p-value <0.001). Lean individuals (BMI< 25kg/m^2) have higher mean NT-proBNP than obese (BMI>25kg/m^2) shown in Figure.

DISCUSSION

This study intended to find the effect of diabetes on plasma NT-proBNP levels in patients with HF. Our data has shown that heart failure patients with already established T2DM have higher levels of NT-proBNP than non-diabetics (15826.08±8143.434 pg/mL and 12534.06±6323.921 pg/mL, respectively). There was a statistically significant difference in NT-proBNP levels between diabetics and non-diabetics t(192)=-3.149, p=0.02. Dal *et al*. conducted a study comprising (n=79) patients with uncontrolled DM to evaluate the relationship between glycemic control and BNP levels. They compred the BNP in the same patients before and after achieving glycemic control and found a significant decrease in BNP levels. Data demonstrated a positive correlation between BNP and HbA1c (r=0.345, p= 0.003).[15] This finding is consistent with ours as our data also showed a positive correlation between two variables in the diabetic group, which is independent of BMI. Thus, diabetic patients have higher NT-proBNP levels as compared to non-diabetics. Similarly, Baldassarre *et al*. demonstrated that diabetic people had a 2.6-fold higher odds ratio of having higher NT-proBNP levels than those without diabetes, independent of body mass index, confounders and risk factors.[16]

Table-III: Pearson's correlation of NT-proBNP with HbA1c and NT-proBNP with NYHA Functional Class in HF patients with or without Diabetes

NT-proBNP			
HbA1c	Diabetics (n=96)	Pearson's coefficient (r)	0.541
		p-value	0.001
	Nondiabetics (n=98)	Pearson's coefficient (r)	0.024
		p-value	0.813
NYHA functional class	Diabetics (n=96)	Pearson's coefficient (r)	0.696
		p-value	0.001
	Nondiabetics (n=98)	Pearson's coefficient (r)	0.683
		p-value	0.001

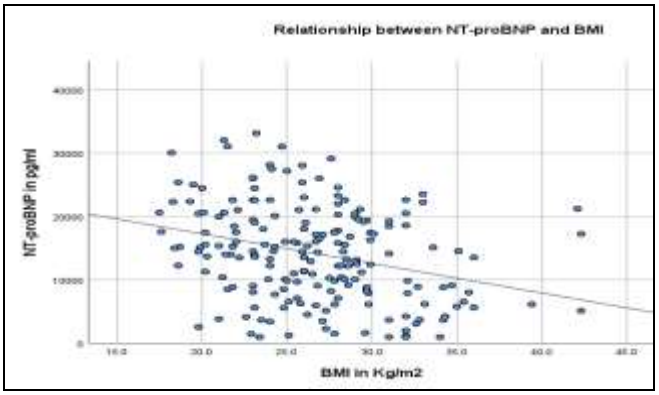

Figure: Relationship between NT-proBNP and BMI in HF patients with and without diabetes mellitus

The inverse relationship between NPs and obesity has been well established. Likewise, our data also showed lower NT-proBNP levels in obese as compared to lean individuals with established heart failure. Thus,

NT-proBNP has a negative correlation with BMI. However, despite this inverse relationship NT-proBNP has a strong positive correlation with the degree of dyspnea in people with diabetes and non-diabetic patients (r=0.696, *p*=0.001 and r=0.683, *p*=0.000, respectively). Yousaf *et al*. conducted at CMH Malir Karachi (n=632) to assess the clinical utility of NT-proBNP in patients with acute dyspnea and demonstrated a positive correlation. Thus, it indicated that it is a reliable cardiac biomarker in patients with CVD.[17] However, we did not find a statistically significant difference in mean NT-proBNP levels of males and females (13920.49±741.572 vs 14386.5±770.49 with *p* =0.664). Although some studies have shown higher NT-proBNP levels in females compared to males, this difference is attributed to the protective effect of sex hormones and recommended gender-specific NP reference ranges.[18] Conversely, many studies have demonstrated no significant difference in NT-proBNP based on gender. Franke *et al*. established that despite the predominance of males in CVD and gender specific differences, the clinical utility of NT-proBNP is equally useful in HF patients both in males and females.[19] This finding is consistent with our observation.

CONCLUSION

Although most diabetic patients are overweight and BMI has a negative impact on NP concentrations, the plasma NT-proBNP is still a very informative tool for the diagnosis and prognosis of HF. Irrespective of BMI, diabetic patients with HF have comparatively higher NT-proBNP levels and showed a moderate positive correla-tion with HbA1c. Our finding also confirmed that the severity of HF can be judged by the concentration of plasma NT-proBNP regardless BMI.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SIJ & MY: Data acquisition, critical review, approval of the final version to be published.

ZHH & MA: Study design, drafting the manuscript, data interpretation, approval of the final version to be published.

MUM & FY: Conception, study design, data analysis, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated & resolved.

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