Research Article

Beyond Heart Failure: role of NT-Pro-BNP in Diabetes mellitus Patients with Preserved Ejection Fraction

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Abstract

Background: Despite advancements in medical care, including coronary interventions and medications, cardiovascular-related mortality and morbidity remain disproportionately high among patients with diabetes mellitus. A significant factor contributing to this issue is the presence of asymptomatic macrovascular and microvascular angiopathies in many diabetic patients. These vascular complications are often detected at later stages, resulting in the failure of treatment strategies to effectively prevent the progression of heart failure and mitigate worsening conditions. Given this background, our research aims to explore the potential of the biochemical marker NT-pro-BNP (N-terminal pro b-type natriuretic peptide) in the early detection of left ventricular diastolic dysfunction in diabetic patients who maintain a preserved ejection fraction. Left ventricular diastolic dysfunction is a condition where the left ventricle has difficulty relaxing and filling with blood, which can precede the development of heart failure. Identifying this dysfunction early could be crucial in preventing major adverse cardiac events (MACE) such as heart attacks, stroke, and cardiovascular-related death.The focus of our study is to determine whether NT-pro-BNP, which is typically elevated in heart failure, can serve as an early marker for diastolic dysfunction in this specific patient population. By identifying diabetic patients at risk earlier, interventions could be tailored more effectively, potentially improving outcomes and reducing the incidence of severe cardiovascular events.

Study population and methods: This study was conducted at a tertiary care medical care hospital in Madurai, Tamil Nadu, India, with a sample population of 500 patients who had preserved ejection fraction. The participants were divided into two groups: 169 diabetic patients and 150 non-diabetic patients. As part of the baseline assessment, routine clinical chemistry analysis and 2D echocardiograms were performed. Additionally, the biomarker NT-pro-BNP, which is associated with heart failure, was measured using the electrochemiluminescence method.

Result: Among the diabetes and non-diabetes groups, the biomarker NT-pro-BNP were significantly different and the serum concentration of NT-pro-BNP was found to be higher in poor glycemic control type 2 diabetes mellitus patients. Serum NT-pro-BNP screening and 2D echocardiogram showed the best predictor of left ventricular diastolic

dysfunction and hospital stay due to major adverse cardiac events in type 2 diabetes mellitus patients.

Conclusion: Our study highlights the clinical significance of NT-pro-BNP among (left ventricular diastolic dysfunction) type 2 diabetes mellitus with preserved ejection fraction > 60 %.

Introduction

Diabetes is the second most common noncommunicable disease burden even in developing countries like India with most of the population falling under moderate workers [1]. Silent myocardial infarction and asymptomatic cardiac remodelling including cardiac myopathies are quite common in diabetes. Because of the availability of advanced cardiac interventions, the mortality associated with heart failure and cardiovascular related complications requiring hospitalization has been increased over the past decade. This has paved the way for emergence of the newer heart failure biomarkers profile over the years to help the treating clinicians in diagnosis as well as prognosis [2]. Since the new biomarkers like NT- pro BNP are not available in all the clinical setup, these are not quite commonly used in the clinical practice. So the diagnosis and monitoring of the prognosis of heart failure is still based on the clinical signs and symptoms, followed by ECHO [2,3].

The heart failure symptoms like breathlessness, pedal edema starts developing after the compensation of cardiac output in a significant level i.e., LVEF<40% that is called as reduced ejection fraction heart failure [4]. Since most of the myocardial infarction in diabetes mellitus will be presenting as silent myocardial infarction, this goes unnoticed. All the cardiac related biomarker profile are expensive to run in a long way and still have a query to pick up the heart failure in early stage before the compromise of left ventricular ejection fraction (LVEF). This results in the search of any one biomarker that might be able to pick up the chances of an individual who will land up in future heart failure especially in diabetes mellitus patients [5]. Have this question in mind, we formulated this study to assess the clinical significance of the NT-pro-BNP analysis in preserved ejection fraction in diabetes patients

Materials and Methodology

After obtaining institutional ethical committee clearance no: VMCIEC/004/2023 in accordance with the Declaration of Helsinki, we retrospectively analysed patients admitted to a tertiary care hospital from January 2022 to July 2024. During this period, 500 patients, both inpatients and outpatients, underwent NT-pro-BNP testing along with echocardiograms. A strict exclusion criterion was applied, excluding patients with chronic kidney disease, anaemia, sepsis, or a reduced ejection fraction of less than 50%. From the total sample of 500 patients, we excluded 181 cases due to conditions such as COPD, CKD, anaemia, structural heart disease, pericarditis, or an ejection fraction less than 60%.

The remaining patients were categorized based on their glycaemic status into two groups: Group 1 (n=169, 61% male and 39% female), which included non-diabetic patients out of which 21 cases were with hypertension and Group 2 (n=150, 63% male and 37 % female), which included diabetic patients out of which 19 cases were with hypertension. The data for this study were sourced from the medical records of Medical College Hospital and Research Institute, Madurai, following approval from the institutional ethical committee.

NT-pro-BNP was analysed using the Cobas e411 by the electro- chemiluminescence method, while all the other routine biochemical parameter were analysed using the TOSHIBA 120 FR fully automated analyser. Echocardiograms was done for comprehensive assessment.

Measurement of NT-pro BNP

NT-pro-BNP levels were measured using the Cobas e411 Elecsys NT-pro-BNP immunoassay (Roche Diagnostics) [1]. The range of measurements of the same was 5 to 35 000 pg/mL with limit of detection 5 pg/mL.

Statistical analysis

Out of 319 total sample population, 169 diabetic patients and 150 non diabetic patient data were statistically tested. In this, there is a significant difference in the NT-pro-BNP level in the diabetic patients compared to non-diabetic patients. There is a positive correlation between the HbA1C level and NT-pro-BNP level in diabetic patients with preserved ejection fraction LVEF > 60.

Table 1: Basic and Biochemical characteristics of study subject.

Variables	Non-diabetes (EF>60%) In median with interquartile range (n=169)	Diabetes (EF>60%) In median with interquartile range (n=150)	p-Value
Age (in years)	59.00 (48.00 - 67.00)	59.00 (51.00 - 67.00)	0.55
FBS (in mg/dl)	88.00 (85.00 - 136.00)	155.00 (133.75 - 200.25)	**0.001**
PPBS (in mg/dl)	116.00 (89.00 - 150.00)	171.00 (125.00 - 250.00)	**0.001**
HbA1C (%)	5.6 (5.3-5.9)	9.8 (8.5-11.5)	**0.001**
NT-pro-BNP (in pg/mL)	131.30 (74.85 - 361.50)	4567.00 (2008.00 - 8925.00)	**0.001**
Cholesterol (in mg/dl)	182.50 (154.00 - 219.00)	177.00 (143.00 - 196.00)	**0.026**
Triglyceride (in mg/dl)	131.00 (89.50 - 179.25)	146.50 (111.25 - 198.00)	0.051
HDL (in mg/dl)	48.00 (43.00 - 52.00)	37.00 (33.00 - 39.00)	**0.001**
LDL (in mg/dl)	118.00 (96.00 - 152.75)	111.50 (86.00 - 135.00)	0.095
Serum creatinine (in mg/dl)	0.400 (0.300 - 0.500)	0.400 (0.300 - 0.575)	0.782
Blood urea (in mg/dl)	18.00 (14.00 - 25.00)	19.50 (15.00 - 24.75)	0.082
Systolic BP (in mm/Hg)	125.00 (115.00 - 135.00)	125.00 (115.00 - 135.00)	0.246
Diastolic BP (in mm/Hg)	80.00 (80.00 - 85.00)	80.00 (80.00 - 90.00)	0.5

The table compares median values with interquartile ranges for age, blood pressure, fasting and postprandial blood sugar levels, and HbA1C between non-diabetes (n=169) and diabetes (n=150) individuals with ejection fraction >60%. The diabetic group shows higher NT pro BNP levels than the non-diabetic group.

Table 2: Correlation of NT-pro-BNP with other parameters among the non-diabetic group and diabetic group.

Variables	Non-Diabetic group		Diabetic group	
	NT-pro-BNP		NT-pro-BNP	
	r value	p value	r value	p value
RBS	0.118	0.353	0.128	0.281
HbA1C	**.961****	**0.000**	**.863****	**0.000**
FBS	-0.016	0.853	-0.056	0.664
PPBS	**0.167**	**0.065**	**.489****	**0.000**
Cholesterol	-0.127	0.098	0.008	0.921
TGL	0.031	0.691	0.031	0.704
HDL	**-.924****	**0.000**	**-.715****	**0.000**
LDL	0.008	0.921	0.038	0.644
Age	**-.209****	**0.006**	**.194***	**0.017**

The table shows the spearman correlation (r value) and significance (p value) of NT-pro-BNP levels with glycemic status and lipid profiles in patients of non-diabetic group and diabetic group. Significant correlations $p < 0.05$ and $p < 0.01$ are indicated with an asterisk (*) and (**) respectively. NT-pro-BNP is significantly correlated with HbA1C, HDL and age in both groups in EF > 60.

Table 3: Regression analysis between non- diabetes and diabetes mellitus group with EF > 60

Group	Diabetes mellitus		Non-Diabetes mellitus	
Variables	**Standardized Beta Coefficients**	**p-Value**	**Standardized Beta Coefficients**	**p-Value**
HbA1C	**0.869**	**0.000**	**0.011**	**0.918**
Cholesterol	0.211	0.086	0.011	0.911
Triglyceride	-0.079	0.145	0.032	0.678
HDL	**0.121**	**0.021**	**-0.485**	**0.000**
LDL	-0.170	0.154	-0.089	0.313
Age	**0.119**	**0.012**	**0.163**	**0.029**
Dependent variable: NT-pro-BNP				

Table 4: Association between variables in good glycemic and poor glycemic control within diabetes mellitus group.

Variables	Diabetic group with good glycemic control with HbA1C cut off < 7 %		Diabetic group with poor glycemic control with HbA1C cut off > 7 %	
	NT-pro-BNP		NT-pro-BNP	
	r value	**p value**	**r value**	**p value**
RBS	-0.327	0.429	0.099	0.431
HbA1C	**.963****	**0.000**	**.855****	**0.000**
FBS	-0.374	0.362	-0.146	0.294
PPBS	**0.314**	**0.377**	**.504****	**0.000**
TGL	-0.174	0.477	0.006	0.944
HDL	-.717**	0.001	-.646	0.090
LDL	0.048	0.854	0.024	0.786
Age	.575*	0.010	0.075	0.393

Discussion

NT-pro-BNP as a Biomarker of Heart Failure

The role of NT-pro-BNP as a biomarker of heart failure severity is supported by studies such as those by Maisel et al. [1] and Januzzi Jr et al. [2]. These studies highlight the rapid measurement and diagnostic utility of NT-pro-BNP in identifying heart failure.

In our study, a significant positive correlation was found between HbA1C and NT-pro-BNP levels in both groups. The strength of this correlation was higher in the diabetic group (r = 0.863, p = 0.000) than in the non-diabetic group (r = 0.961, p = 0.000), suggesting that chronic hyperglycaemia, as reflected by elevated HbA1C advanced glycated end product, has a direct impact on NT-pro-BNP levels. The relationship between HbA1C and NT-pro-BNP suggests that poor glycemic control exacerbates cardiac stress, even in patients with preserved ejection fraction. These findings align with previous mentioned studies that report increased NT-pro-BNP levels in diabetic patients, likely due to the combined effects of hyperglycemia, insulin resistance, and other metabolic factors that contribute to myocardial dysfunction. It's essential to note potential molecular overlaps with insulin and cyclic guanosine monophosphate (cGMP) pathways. In diabetic cardiomyopathy, insulin resistance disrupts normal insulin signalling pathways, leading to impaired glucose uptake and utilization [3]. This disruption may contribute to cardiac dysfunction and remodelling, enhancing the release of NT-pro-BNP as a compensatory mechanism [4].

Association with Diabetic Cardiomyopathy

Studies by Jia et al. [5] and Marwick et al. [6] provide evidence for the association between NT-pro-BNP elevation and diabetic cardiomyopathy. These authors emphasize the distinct nature of cardiac dysfunction in diabetes, independent of other cardiovascular risk factors.

Molecularly, chronic hyperglycemia and insulin resistance activate pathways such as the renin-angiotensin system (RAS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to increased oxidative stress [7]. This oxidative stress contributing to cardiac remodelling and dysfunction characteristic of diabetic cardiomyopathy, possibly augmenting NT-pro-BNP release [8] supported our findings that in the

diabetic group, NT-pro-BNP also correlated significantly with postprandial blood sugar (PPBS, r = 0.489, p = 0.000) and negatively with HDL (r = -0.715, p = 0.000). These correlations suggest that both glycemic variability and dyslipidemia contribute to cardiac strain in diabetic patients. The negative correlation between HDL and NT-pro-BNP in both groups indicates that lower HDL levels, a marker of poor lipid control, are associated with higher NT-pro-BNP, reinforcing the role of dyslipidemia in cardiovascular risk.

Subclinical Heart Dysfunction in Diabetes

This study highlights a significant difference in NT-pro-BNP levels between diabetic and non-diabetic patients, particularly in individuals with preserved ejection fraction (LVEF > 60%). Diabetic patients exhibited markedly higher NT-pro-BNP levels compared to non-diabetics, suggesting that diabetes plays a critical role in elevated NT-pro-BNP levels, which may indicate subclinical cardiac stress even in the absence of reduced ejection fraction. Fang et al. [9] and Seferović and Paulus et al. [10] discuss the presence of subclinical cardiac dysfunction in diabetes, even in the absence of overt heart failure symptoms. Elevated NT-pro-BNP levels may serve as an early indicator of such dysfunction.

Molecularly, dysregulated insulin signalling and increased oxidative stress contribute to mitochondrial dysfunction and impaired calcium handling in cardiomyocytes [11]. These molecular alterations may precede clinical manifestations of heart failure, highlighting the importance of NT-pro-BNP as a marker of subclinical dysfunction [12].

Implications for Risk Stratification

In our study, the subgroup analysis of diabetic patients with good and poor glycemic control, the correlation between HbA1C and NT-pro-BNP remained significant in both groups (r = 0.963, p = 0.000 in good control, and r = 0.855, p = 0.000 in poor control). However, the correlation with PPBS was only significant in the poor glycemic control group (r = 0.504, p = 0.000), suggesting that glycemic fluctuations may contribute more to cardiac stress in patients with poor long-term glycemic control.

Huelsmann et al [9] and Anand et al. [10] emphasize the potential of NT-pro-BNP levels for risk stratification in diabetic patients. Elevated levels may indicate a higher risk of cardiovascular complications. At the molecular level, dyslipidemia and chronic hyperglycemia activate pathways such as PPAR alpha and CD36, leading to increased fatty acid uptake and oxidative stress in cardiomyocytes [7]. These processes may exacerbate cardiac dysfunction and increase NT-pro-BNP release, underscoring its utility in risk stratification [9].

Additionally in this study, we also found that age was another significant predictor in both groups, though its influence was more pronounced in the non-diabetic group (β = 0.163, p = 0.029). This suggests that while age plays a role in cardiac stress across the board, diabetes has a more substantial impact on NT-pro-BNP levels, independent of age.

Potential Mechanisms

In this study, Regression analysis demonstrated that HbA1C was the most significant predictor of NT-pro-BNP levels in diabetic patients (β = 0.869, p < 0.001), underscoring the importance of glycemic control in managing cardiac stress.

Marwick TH et al. [4] and Bugger and Abel [8] elucidate the molecular mechanisms underlying diabetic cardiomyopathy. They describe how insulin resistance, oxidative stress, and mitochondrial dysfunction contribute to cardiac remodelling and dysfunction.

Specifically, dysregulated insulin signalling and increased fatty acid oxidation lead to mitochondrial dysfunction and impaired ATP production. This disrupts normal cardiac function and may contribute to NT-pro-BNP release as a compensatory response.

Clinical Relevance and Treatment Implications

Overall, the findings in our study suggested that NT-pro-BNP levels are strongly influenced by glycemic control and lipid profiles in diabetic patients and that targeting both glycemia and dyslipidemia may be crucial for reducing cardiovascular risk in this population. The strong correlation between HbA1C and NT-pro-BNP highlights the importance of maintaining tight glycemic control to prevent cardiac dysfunction, even in patients with preserved ejection fraction. These results emphasize the need for comprehensive management strategies addressing both metabolic and cardiovascular health in diabetic patients. The same finding was quoted by McMurray et al. [11] and Yancy et al. [12] discussed the clinical implications of elevated NT-pro-BNP levels in diabetic patients. They highlight the importance of aggressive risk factor management and lifestyle modifications in mitigating cardiovascular risk.

Molecularly, pharmacological interventions targeting pathways such as the RAS and oxidative stress may attenuate cardiac dysfunction and reduce NT-pro-BNP release. These interventions could complement traditional management strategies in diabetic patients.

Conclusion

NT-pro-BNP is a better marker in preserved ejection fraction with diastolic dysfunction, concurrent and hence evaluation with NT-pro-BNP along with ECHO evaluation will help in evaluating the diastolic dysfunction. During diastole i.e., ventricular relaxation, coronary perfusion to endocardium as well as myocardium more, in case of diastolic dysfunction where the relaxation doesn't effectively occur. So elevated levels of NT-pro-BNP, a cardiac neurohormone in diastolic dysfunction with preserved ejection > 60% will help us to find out myocardial

ischemic risk in early, especially in diabetes mellitus where the silent myocardial infarction, heart failure and sudden cardiac death occurring commonly.

Conflict of interest

There is no conflict of interest.

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