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Determining the role of NT-proBNP levels in diabetic patients with heart failure: A study from North India

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Abstract:

BACKGROUND: Diabetic patients are at higher risk of cardiovascular morbidity and mortality. NT-proBNP levels measurements are useful for the assessment of risk in heart failure patients in emergency condition and give the faster result. Further, it also offers lower cost and unnecessary hospitalization and follow-up cost. The studies have shown that NT-proBNP levels are a direct predictor of outcome risk in diabetic patients with heart failure. The objective of this research was to study the role of NT-proBNP levels to determine the severity of heart failure in diabetic patients.

MATERIALS AND METHODS: In this study 150 patients diagnosed with symptomatic heart failure admitted to the emergency department of a tertiary care center from January 2021 to January 2022 have been included in Saraswati Institute Of Medical Sciences, Hapur, India. N-terminal pro-B-type natriuretic peptide (NT-Pro-BNP) levels were measured using an automated analyzer ranging between 60 and 3000 pg/ml. According to the European society of cardiology (ESC) guidelines, it has been defined as NT-Pro-BNP level above 125 pg/ml indicates a high possibility of heart failure and NT-Pro-BNP level below 125 pg/ml excludes the high possibility of heart failure. All the patients underwent an echocardiographic study and ejection fraction was calculated and recorded.

RESULTS: In diabetic patients ejection fraction was significantly lower in diabetic patients: 47.15 ± 8.75% vs. 43.24 ± 9.54%, $P = 0.002$). We have observed statistically significant lower HDL values (40.10 ± vs. 35.94 mg/dL, $P = 0.0004$), however, significant higher triglycerides values were found (101.43 ± 41.7 mg/dL vs. 151.37 ± 78.85, $P = 0.001$). No significant difference was observed in LDL level (97.8 ± 31.23 vs. 92.35 ± 314.2, $P \geq 0.05$) and total cholesterol level (161.49 ± 41.38 vs. 159.97 ± 41.12, $P \geq 0.05$).

CONCLUSION: We concluded that the measurement of NT-proBNP in heart failure and diabetic patients could be an economic marker for the evaluation of morbidity and mortality, facilitating better management and follow-up.

Keywords:

Diabetes mellitus, heart failure, NT-proBNP

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Introduction

One of the most significant chronic diseases today is type 2 diabetes mellitus (T2DM), which has been linked to both small- and large-scale vascular issues, as well as numerous adverse effects. There has been a reported rise in the death rate from organ dysfunctions brought on by macrovascular and microvascular diseases.[1] Type 2 diabetes mellitus (T2DM) has a strong correlation with the emergence of chronic heart failure (HF).[2] Patients with T2DM have a 4 times higher frequency of HF than the overall population. T2DM can cause HF through a variety of pathways, including fibrosis, low-grade inflammation, oxidative stress, and endothelial dysfunction.[3] These mechanisms result in myocardial ischemia,

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accelerated atherosclerosis, increased vascular stiffness, and diabetic cardiomyopathy. Diabetic patients are at higher risk of cardiovascular morbidity and mortality.[4] It has been shown that around 30–40% of the diabetic patients are associated with cardiovascular complications. At the same time, among diabetic patients, women are more at risk of developing HF as compared to men.[5-9] To enhance the prediction of HF incidence and its progression, several biomarkers have been explored in order to better understand how HF develops in people with type 2 diabetes. Nevertheless, due to vague symptoms in HF patients and a lack of a "gold standard" approach for a precise diagnosis, the 2008 European recommendations emphasize natriuretic peptides' potential value as HF markers.[10] N-terminal product derived (NT-proBNP) is a cardiac hormone released by the myocardium in response to increased pressure and volume. Most studies have stated that NT-proBNP levels are predictors of cardiovascular changes and their complications.[10] Earlier studies have shown that N-terminal product derived (NT-proBNP), neuro-hormone, can help not only in early diagnosis but also in the treatment and prognosis of the patients with HF.[11,12] It has been seen that HF patients are repeatedly sent for echocardiography for diagnosis; however, echocardiography is hardly possible in resource-limited settings. NT-proBNP levels measurements are useful for the assessment of risk in HF patients in emergency conditions and give the faster result. Further, it also offers lower cost and unnecessary hospitalization and follow-up cost. To, the best of our knowledge, pockets of studies are there, aiming at the role of NT-proBNP in diabetic patients with HF. The studies have shown that NT-proBNP levels are a direct predictor of outcome risk in diabetic patients with HF. The objective of this research was to study the role of NT-proBNP levels to determine the severity of HF in diabetic patients. Although it has not yet been implemented in clinical practise, NT-proBNP enhances the discriminatory capability of risk-prediction models in type 2 diabetes mellitus (T2DM). In high-risk T2DM patients, the study evaluated the discriminatory power of NT-proBNP alone for death and cardiovascular events.

Materials and Methods

Study design and setting

In this study, 150 patients diagnosed with symptomatic HF based on New York Heart Association functional classification (NYHA) class II–IV admitted to the emergency department of a tertiary care center from January 2021 to January 2022 have been included in Saraswati Institute of Medical Sciences, Hapur, India and were retrospectively analyzed.[12] HF was defined according to European society of cardiology (ESC) criteria and other cardiovascular risk factors were recorded. Patients with COPD, sepsis, pulmonary embolism, and hyperthyroidism were excluded from our study.

Study participants and sampling

All enrolled 150 patients underwent investigations like blood sugar and N-terminal pro-B-type natriuretic peptide (NT-Pro-BNP) level. Venous blood samples were collected in sodium fluoride and plain test tubes. Serum and plasma were separated as per standard protocol. Serum TGs, TC, LDL, and HDL were determined by enzymatic methods using an automated analyzer. Blood sugar levels were measured by enzymatic methods using an automated analyzer. Diabetes mellitus was defined using American Diabetes Association criteria: fasting plasma glucose levels ≥126 mg/dL or 2-hour plasma glucose levels ≥200 mg/dL or random plasma glucose levels in a patient ≥200 mg/dL.[12,13] NT-Pro-BNP levels were measured using an automated analyzer ranging between 60 and 3000 pg/ml. According to the ESC guidelines, it has been defined as NT-Pro-BNP level above 125 pg/ml indicates the high possibility of HF, and NT-Pro-BNP level below 125 pg/ml excludes the high possibility of HF.[14] All the patients underwent an echocardiographic study and ejection fraction was calculated and recorded.

Data collection tool and technique

The data collected were analyzed using the STATA/SE version 14.0 statistical software (Stata Corp, Texas, USA). Categorical data were described using numbers and percentages. Data generated from the present study have been presented in the form of tables and all descriptive analyses have been shown in percentages. Data were expressed as mean ± standard deviation. For comparative statistics between two groups, Mann–Whitney U tests and $\chi 2$ test were used. Karl Pearson's correlation coefficient was used to study correlations. *P*-value has been calculated to analyze statistical significance.

Ethical consideration

This was a retrospective study.

Results

A total of 150 patients (n = 150) were included in the present study. Among these 150 patients, 46% were males and 54% were females with a mean age of 68 ± 10 years. Among 150 patients, 45.33% were known diabetics. There was no significant difference observed between the groups concerning sex distribution—male 44.89% vs. 41.45% ($P > 0.05$); female 51.01% vs. 52.01% ($P > 0.05$). In diabetic patients, ejection fraction was significantly lower in diabetic patients: 47.15 ± 8.75% vs. 43.24 ± 9.54%, P = 0.002. We have observed statistically significant

lower HDL values (40.10 ± vs. 35.94 mg/dL, $P = 0.0004$), however, significant higher triglycerides values were found (101.43 ± 41.7 mg/dL vs. 151.37 ± 78.85, $P = 0.001$). No significant difference was observed in LDL level (97.8 ± 31.23 vs. 92.35 ± 314.2, $P \geq 0.05$) and total cholesterol level (161.49 ± 41.38 vs. 159.97 ± 41.12, $P \geq 0.05$). The mean value of NT-Pro-BNP in both groups was 2678 ± 2765.21 pg/ml: 2446 ± 2615 pg/ml in patients without diabetes and 2582 ± 2780.12 in patients with diabetes mellitus. Significant correlation was observed in NT-Pro-BNP level with the following parameters: triglycerides (rho = −0.238. $P = 0.002$), total cholesterol (rho = −0.13, $P = 0.037$), and ejection fraction (rho = −0.361, $P = 0.001$). Negative correlation between NT-Pro-BNP level and ejection fraction has been observed irrespective of blood glucose level (r = −0.326, $P = 0.0001$ vs. r = −0.248, $P = 0.0001$). In both diabetic vs. non-diabetic groups uni- and multivariate analyses were used to determine the determinants of NT-Pro-BNP. In case of diabetic patients, significant correlation has been observed between NT-Pro-BNP and ejection fraction (rho = −0.397, $P = 0.0001$), triglycerides (rho = −0.183, $P = 0.01$), and total cholesterol (rho = −0.31, $P = 0.049$). Further, by using multivariate analyses, we have observed that triglycerides ($P = 0.0281$) and ejection fraction ($P = 0.0002$) are independent predicative factors for increased NT-Pro-BNP levels. In the case of men with diabetes mellitus, NT-Pro-BNP level showed a significant correlation with triglycerides (rho = −0.35, $P = 0.02$) and ejection fraction (rho = −0.467, $P = 0.0076$), however, on multivariate analyses, only ejection fraction was found to be independent predictive factor for NT-Pro-BNP level. Further, for diabetic women, NT-Pro-BNP level correlated well with ejection fraction (rho = −0.346, $P = 0.0039$) and ejection fraction being the independent determinant. In non-diabetic men, NT-Pro-BNP level had a significant correlation with HDL cholesterol (rho = −0.43, $P = 0.04$), total cholesterol (rho = −0.37, $P = 0.021$), and ejection fraction (rho = −0.54, $P = 0.0001$). In case of non-diabetic women, NT-Pro-BN*P* values were well correlated with triglycerides (rho = −0.35, $P = 0.005$), LDL cholesterol (rho = −0.179), $P = 0.038$), and total cholesterol (rho = −0.237, $P = 0.005$) but only total cholesterol ($P = 0.013$) was found to be an independent predictive factor. However, in case of diabetic counterparts on multivariate analysis, ejection fraction has proven to be an independent determinant. In non-diabetic patient with HF NT-Pro-BNP levels have shown a positive correlation with triglycerides (rho = −0.216, $P = 0.001$), HDL cholesterol (rho = −0.285, $P = 0.003$), LDL cholesterol (rho = −0.31, $P = 0.004$), total cholesterol (rho = −0.349, $P = 0.001$), and ejection fraction (rho = −0.381, $P = 0.002$). Only total cholesterol ($P = 0.0045$), LDL cholesterol ($P = 0.0387$), and ejection fraction ($P = 0.0159$) were found to be independent predictors of NT-Pro-BNP level on multivariate analysis.

Discussion

Ruben originally identified diabetic cardiomyopathy in 1972 while doing post-mortem exams on four diabetic patients. When there was no other cardiovascular illness present, their hearts had severe myocardial hypertrophy and fibrosis.[15] Left ventricular dysfunction in diabetic patients without a history of hypertension, ischemic heart disease, or severe valve disease is now considered to be diabetic cardiomyopathy. It is currently unclear what pathophysiological process results in diabetic cardiomyopathy. Diastolic dysfunction is caused by a variety of factors, including altered lipid metabolism, cardiac lipid accumulation, oxidative stress, mitochondrial dysfunction, inflammation, and RAAS activation.[16] These factors eventually cause myocardial hypertrophy, apoptosis, and necrosis, which in turn cause diastolic dysfunction.

The main finding in our study was that the mean age of the patients was 68 ± 10 years. Among 150 patients, 45.33% were known diabetic. Similar, to our study researchers have reported mean age of 71.2 ± 9.14 for diabetic patients with HF.[17] In individuals over 65 years old, another study found that the prevalence of DM was substantially lower (about 22%).[18] In addition to diabetes mellitus other risk factors such as dyslipidemia, obesity, metabolic syndrome, and hypertension also play important role in the evolution of HF.[16] The presence of diabetes is usually correlated with systemic arterial hypertension. According to studies, more than 71% of diabetic individuals also have concurrent arterial hypertension.[19] Given the rising prevalence of hypertension globally,[20] Romania has a prevalence of about 63%.[20] In consistent to a previously published study 71.5% of patients were hypertensive in our study.[17,18] For the evolution of HF, dyslipidemia is another important risk factor in diabetic patients. Clearly, the overall cardiovascular risk increases when numerous risk variables are present.[21] Around 81% of DM patients in Romania also had concurrent dyslipidemia.[20] The significant association was observed with high triglycerides values and lower HDL values in diabetic patients, however, no significant association was seen between LDL cholesterol and total cholesterol levels in the two groups. Similar significant association between diabetes and dyslipidemia has been seen in a previous study from Romania.[19] As a result, we examined not just the relationship between other prevalent cardiovascular risk factors but also the most significant HF biomarker, NT-proBNP. It is important to note that NT-Pro-BNP is still a reliable predictor of unfavorable cardiovascular events in diabetes persons without cardiovascular disease.[22] In the present study, we have analyzed the role of NT-proBNP levels to determine the severity of HF in diabetic patients. Several authors have reported

that NT-proBNP is a prognostic marker of mortality and morbidity in HF patients. This neuropeptide can be used to identify diabetic patients who need primary preventive interventions, as demonstrated by the PONTIAC experiment.[23] We have also analyzed the role of NT-proBNP as a biomarker, other associated powerful risk factors and their relationship with ejection fraction. No significant difference was observed between NT-proBNP mean values in patients with or without diabetes. We also found a significant association between NT-proBNP and ejection fraction in diabetic women, further, the negative correlation was observed in between these parameters in other groups. However, in patients with diabetes positive correlation was found between ejection fraction, triglycerides, and total cholesterol. Ejection fraction and triglycerides level were found to be independent predictor for NT-proBN*P* values. In non-diabetes patients with HF, significant correlation was found between ejection fraction, triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol. In contrast to our study, previous studies have shown inverse relation to above stated lipid parameter.[24] Previously published article has demonstrated that low level of cholesterol is an independent predictor of NT-proBNP level.[25] In non-diabetic patients, total cholesterol and LDL cholesterol were independent predictor of NT-proBNP level in contrast to diabetic patients where triglycerides were also an independent determinant. About 28% of patients with HF and a maintained EF had DM. Due to population aging, the correlation between the two comorbidities is always increasing. The link between DM and HF is reciprocal, meaning that each condition raises the likelihood of developing the other. In this study, diabetic patients with HF had a mean EF that was considerably lower than that of patients without DM. It goes without saying that diastolic dysfunction raises the end-diastolic pressures in the left ventricle, which raises the left atrial pressure and increases the risk of atrial fibrillation. In the present study, ejection fraction was less in the diabetic group as compared to the non-diabetic group similar observation was found in the previously published article.[26,27] NT-proBNP level has the same diagnostic and prognostic value in diabetic patients with HF and non-diabetic patients. Though NT-proBNP levels did not differ significantly between non-diabetic and diabetic group, NT-proBNP still holds a critical role in the evaluation of HF and diabetic patients.

Limitation and recommendation

This was a single-centric study with a small sample size, and only in-patients were enrolled. We did not find a similar study in India that compares NT-proBNP levels in diabetic patients with HF. This study recommends that more province-wise study is required on the role of the measurement of NT-proBNP in HF and diabetic patients as an economic marker for evaluation of morbidity and mortality to facilitate the better management and follow-up.

Conclusion

Although NT-Pro-BNP readings in diabetic patients were not statistically different from non-diabetics, this biomarker nevertheless plays a crucial role in the assessment of individuals with HF and DM, enabling the development of proper care and follow-up. We concluded that the measurement of NT-proBNP in HF and diabetic patients could be an economic marker for the evaluation of morbidity and mortality, facilitating the better management and follow-up.

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Conflicts of interest

There are no conflicts of interest.

References

1. Tol A, Pourreza A, Shojaeezadeh D, Mahmoodi M, Mohebbi B. The assessment of relations between socioeconomic status and number of complications among type 2 diabetic patients. Iran J Public Health 2012;41:66-72.
2. Congenital Heart Disease In the Adult. In: Kasper DL, Braunwald E, Hauser S, Longo D, Jameson JL, Fauci AS (Eds.). Harrison's Principles of Internal Medicine, 16th ed. McGraw-Hill; New York, 2005, p. 1381-1389.
3. Senior R, Galasko G, McMurray JV, Mayet J. Screening for left ventricular dysfunction in the community: Role of hand held echocardiography and brain natriuretic peptides. Heart 2003;89(Suppl 3):iii24-8.
4. Domanski M, Krause-Steinrauf H, Deedwania P, Follmann D, Ghali JK, Gilbert E, *et al*. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. J Am Coll Cardiol 2003;42:914-22.
5. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, *et al*. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. Eur Heart J 2008;29:1224-40.
6. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979;241:2035-8.
7. Cubbon RM, Adams B, Rajwani A, Mercer BN, Patel PA, Gherardi G, *et al*. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology. Diab Vasc Dis Res 2013;10:330-6.
8. Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, *et al*. Diabetes mellitus, a predictor of morbidity and mortality in the studies of left ventricular dysfunction (SOLVD) trials and registry. Am J Cardiol 1996;77:1017-20.
9. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, *et al*. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: An analysis of the Candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) programme. Eur Heart J 2008;29:1377-85.

10. Maries L, Manitiu I. Diagnostic and prognostic values of B-type natriuretic peptides (BNP) and N-terminal fragment brain natriuretic peptides (NT-pro-BNP). Cardiovasc J Afr 2013;24:286-9.
11. Corteville DC, Bibbins-Domingo K, Wu AH, Ali S, Schiller NB, Whooley MA. N-terminal pro-B-type natriuretic peptide as a diagnostic test for ventricular dysfunction in patients with coronary disease: Data from the heart and soul study. Arch Intern Med 2007;167:483-9.
12. Chung IH, Yoo BS, Ryu HY, Wang HS, Choi HM, Kim JY, *et al*. The relationship between the early follow-up BNP level and congestive status or prognosis in acute heart failure. Korean Circ J. 2006;36:200-7.
13. Lim TK, Hayat SA, Gaze D, Celik E, Collinson P, Senior R. Independent value of echocardiography and N-terminal pro-natriuretic peptide for the prediction of major outcomes in patients with suspected heart failure. Am J Cardiol 2007;100:870-5.
14. Marathe PH, Gao HX, Close KL. American diabetes association standards of medical care in diabetes 2017. J Diabetes 2017;9:320-24.
15. Miki T, Yuda S, Kouzu H, Miura T. Diabetic cardiomyopathy: Pathophysiology and clinical features. Heart Fail Rev 2013;18:149-66.
16. Seferović PM, Milinković I, Ristić AD, Seferović Mitrović JP, Lalić K, Jotić A, *et al*. Diabetic cardiomyopathy: Ongoing controversies in 2012. Herz 2012;37:880-6.
17. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al*. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J 2016;37:2129-2200.
18. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes Care 2004;27:699-3.
19. National Diabetes Statistics Report 2017. Available from: http://www.cdc.gov/diabetes/data/statistics/2014StatisticsReport.html. [Last accessed on 2017 Nov 30].
20. Mota M, Popa SG, Mota E, Mitrea A, Catrinoiu D, Cheta DM, *et al*. Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. J Diabetes 2016;8:336-44.
21. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: A comparative risk assessment. Lancet Diabetes Endocrinol 2014;2:634-47.
22. Saeed A, Ballantyne CM. Assessing cardiovascular risk and testing in type 2 diabetes. Curr Cardiol Rep 2017;19:19.
23. Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, *et al*. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): A prospective randomized controlled trial. J Am Coll Cardiol 2013;62:1365-72.
24. Sitar Taut AV, Pop D, Zdrenghea DT. NT-proBN*P* values in elderly heart failure patients with atrial fibrillation and diabetes. J Diabetes Complications 2015;29:1119-23.
25. Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T, *et al*. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: A scientific statement from the American heart association. Circulation 2016;134:e535-78.
26. Yoon CH, Youn TJ, Ahn S, Choi DJ, Cho GY, Chae IH, *et al*. Low serum total cholesterol level is a surrogate marker, but not a risk factor, for poor outcome in patients hospitalized with acute heart failure: A report from the Korean heart failure registry. J Card Fail 2012;18:194-1.
27. Ribeiro A, Lourenço P, Silva S, Cunha F, Vilaça J, Gomes F, *et al*. Predictors of natriuretic peptide non-response in patients hospitalized with acute heart failure. Am J Cardiol 2015;115:69-74.