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Serum NT-proBNP levels in diabetes and its association with obesity, inflammation and glycemic status

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) patients are more prone to develop cardiovascular complications, and there is a dire need of a routine screening tool for risk assessment of heart failure (HF) in them. **Aims and Objectives:** The current study was conducted to estimate the levels of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in subjects with and without T2DM and evaluate the association between NT-proBNP and body mass index (BMI), waist circumference as markers of obesity, hemoglobin A1c (HbA1c), plasma fasting blood sugar (FBS), plasma postprandial blood sugar (PPBS),duration of diabetes as markers of glycemic control and serum C-reactive protein (CRP),an inflammatory marker in diabetic subjects. **Materials and Methods:** A hospital-based cross-sectional non-interventional study was done with 82 non-diabetic healthy volunteers and 82 T2DM patients. Anthropometric measurements (waist circumference [WC] and body mass index [BMI]) were recorded, and blood was analyzed for serum NT-proBNP, C-reactive protein (CRP), plasma fasting blood sugar (FBS), postprandial blood sugar (PPBS), and hemoglobin A1c (HBA1c). Data collected were analyzed by statistical software with $P<0.05$ as the significance level. **Results:** Serum NT-proBNP level was significantly higher in diabetic group ($P<0.001$) compared to non-diabetic group statistically. Correlation analysis in diabetic subjects showed a significant positive correlation of NT-proBNP with CRP ($\rho+0.576$, $P<0.001$), duration of diabetes ($\rho+0.780$, $P<0.001$), plasma FBS ($\rho+0.524$, $P=0.003$), plasma PPBS ($\rho+0.673$, $P=0.013$), and HbA1c ($\rho+0.571$, $P=0.001$) but there was no statistically significant correlation of NT-proBNP with BMI or WC values although the correlation was negative for both. **Conclusion:** The present study provides a novel perspective that measuring serum NT-proBNP may help in the earlier identification of impending HF in diabetic individuals assisting in prompt intervention which may be further confirmed by larger studies.

Key words: N-terminal pro-B-type natriuretic peptide; C-reactive protein; Type 2 diabetes mellitus

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INTRODUCTION

Diabetes mellitus (DM) is a large public health problem which affects about 537 million individuals according to the International Diabetic Federation 2021. This number is projected to rise to 643 million by 2030.[1] The number of diabetic patients in India is estimated to be 74.2 million in 2021, and this is likely to reach 124.8 million in 2045.[1]

Diabetes patients with uncontrolled blood glucose are at high risk of microvascular and macrovascular complications.[2] The most evident cardiac complication is coronary atherosclerosis.[3] Heart failure (HF) is a common cardiovascular complication both in diabetic and non-diabetic population which increases with aging. Screening for kidney and retinal complications is already an established part of routine diabetes care today, but there is no comparable reoccurring screening for cardiac

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complications of diabetes.[2] This may simply be due to the lack of cost-effective methods and expertise as an echocardiographic examination being both expensive and time-consuming is not suited for screening purposes.

Diabetes is more prevalent among HF patients. A recent study suggested that among the HF patients hospitalized, 44% have DM.[4] In the Framingham study, it was concluded that male diabetic patients and female diabetic patients had twice the risk and 5 times the risk, respectively, to develop HF compared to control population.[5] The clarification behind this fact may be the increase in incidence and severity of ischemic heart disease among diabetic patients. Moreover, diabetic patients have a disproportionate increase in left ventricular mass independent of hypertension and in some autopsy study increased collagen content was found in heart of diabetic patients.[6] All of these factors may contribute to increased myocardial stiffness.

Breakthrough advances have been made in the diagnostic field and management guidelines of HF in recent years. Cardiac biomarkers are an essential tool for clinicians. Brain natriuretic peptide (BNP), a 32-amino acid peptide, is synthesized predominantly in the left ventricle of the heart as the 108-amino acid prohormone prepro BNP.[7] The hormone stored in the human cardiac tissue, mainly ventricular walls, is a potent vasodilator and a natriuretic factor regulating salt and water homeostasis which is released due to decreased oxygen supply, acute myocardial infarction, chronic cardiac HF, and hypertrophy of the heart.[8] BNP and its N-terminal counterpart (NT-proBNP) are well-established biomarkers used in the diagnosis and prognostic assessment of HF[9] patients and to distinguish cardiac from non-cardiac causes of dyspnea according to the latest European Society of Cardiology (ESC) guidelines.[10] Of note, the cutoff values for chronic presentation BNP/NT-proBNP levels <35 and <125 ng/L are recommended as diagnostic criteria (rule-in cutoff values) for two specific HF categories, namely HF with mid-range ejection fraction (EF) with EF – 40–49% and HF with preserved EF with EF ≥50%.[11]

Some studies revealed that patients of type 2 diabetes mellitus (T2DM) have a significantly higher value of NT-proBNP compared to non-diabetic subjects.[12,13] To the contrary, it was concluded in a prospective study that peripheral NT-proBNP was inversely related to the risk of developing type 2 diabetes in healthy subjects, particularly women, but higher concentrations of it were associated with a higher risk of macrovascular and microvascular disease in people who develop diabetes.[14] Such contrasting views and the scarcity of such studies among the local population have compelled us to design this study. It was hypothesized that assessing the levels of serum NT-proBNP may be instrumental in the identification of risk for HF in diabetic subjects. This cross-sectional study was conducted with the objective to evaluate the alteration of serum NT-proBNP concentrations in subjects with and without T2DM and assess any relationship between NT-proBNP with obesity, inflammation and glycemic status in a population from eastern India.

Aims and objectives

- To measure Serum NT-proBNP, Body mass index (BMI), Waist circumference as markers of obesity, Hemoglobin A1c (HbA1c), Plasma Fasting blood sugar (FBS) and Plasma Postprandial blood sugar (PPBS) as markers of glycemic control, Serum C-reactive protein (CRP), an inflammatory marker in diabetic and non-diabetic individuals
- To compare serum levels of NT-proBNP and CRP between above mentioned groups.
- To find any association between serum NT-proBNP and duration of diabetes, BMI, HbA1c, FBS, PPBS, CRP values in diabetic individuals.

MATERIALS AND METHODS

A hospital-based cross-sectional study was done for 1-year duration after obtaining the approval from the institutional ethics committee. The study population included adult diabetic patients attending the general medicine outpatient department and diabetic clinic of the institution as cases. The control group was selected from the accompanying healthy relatives of the patients after they were age and sex matched. Biochemical investigations and result analysis were performed in the department of biochemistry of the institution. Following inclusion and exclusion criteria, 82 cases and 82 controls, 41 males and 41 females in both groups, were selected by the method of convenience and after obtaining informed consent and institutional ethical clearance.

Inclusion criteria of cases

The following criteria were included in the study:

- The age of the subjects was >18 years
- Individuals who consented to the study
- Individuals diagnosed with T2DM as per guidelines[15] who can perform 6-min walking test.[16]

Exclusion criteria of cases

The following criteria were excluded from the study:

- Uncontrolled hypertension
- Chronic renal failure
- Acute inflammation and sepsis
- On cytotoxic drug, valvular heart disease, myopathy of any kind, and pulmonary hypertension
- On HF medication such as diuretics and ace inhibitors

Controls were selected after proper consent from healthy non-diabetic individuals who can perform 6-min walking test and without any other metabolic diseases, hematological diseases as well as any chronic or active inflammation and infection.

Ethical considerations

Institutional ethical clearance was obtained as per guidelines from the Helsinki Declaration, 1975, as revised in 1983 and was initiated after obtaining the approval of the institutional ethical committee. Written and informed consent was obtained from participants as per protocol.

Data collection procedure

Blood was collected from the subjects in plain clot vial for serum NT-proBNP and serum C-reactive protein (CRP) estimation, ethylenediaminetetraacetic acid vial for hemoglobin A1c (HbA1c) estimation, and fluoride vials for fasting plasma glucose and postprandial plasma glucose analysis after proper preparation of patients at definite schedules. Waist circumference (WC), weight, height, 6-min walking test, and blood pressure were recorded along with a clinical history. After centrifugation, serum was harvested for the specific estimations. The data collected were then analyzed by statistical tests.

Analytes measured:

a. Serum NT-pro was done by chemiluminescent immunoassay (CLIA) method in Advia Centaur Cp immunoassay system. The manufacturer indicated that the recommended clinical thresholds are 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older.
b. Plasma fasting blood sugar (FBS) and postprandial blood sugar (PPBS) were measured by glucose oxidase peroxidase method, HBA1c by antigen-antibody agglutination method, and serum CRP was measured by turbidimetric method using the Konelab system pack reagent and Thermo Fisher Scientific Konelab Prime 60i autoanalyzer. The manufacturer indicated the normal values of up to 6 mg/L for CRP in healthy adults. All reagents and procedures were pre-validated. Quality control of the CLIA kits and enzymatic methods was monitored through the calibrators and control materials.

Statistical analysis

The data obtained from the above parameters were analyzed for differences between the medians of the serum NT-proBNP and CRP of cases and controls by the Mann–Whitney U test as the data failed the Shapiro–Wilk normality tests. Spearman correlation analyses were done between serum NT-proBNP and FBS, PPBS, HBA1c, duration of diabetes, CRP , Body mass index (BMI), Waist ircumference (WC). All statistical analyses were carried out using the IBM SPSS Statistics 26.0 software with $P<0.05$ as the significance level.

RESULTS

The comparison of means of serum analytes between cases and controls in Table 1 and Figure 1 revealed that serum NT-proBNP is significantly high in the diabetic subjects (median 116.5 pg/mL) compared to (median 56.0) controls ($P<0.001$*). There was a statistically significant difference in serum CRP levels between the case (median 7.4 mg/dL) and control groups (median 2.8 mg/dL), the median being higher in diabetic subjects ($P<0.001$*). In the present study, 45.15% (37 out of 82) of diabetic patients were found to have NT-proBNP >125 pg/mL whereas only 4.8% (4 out of 82) of non-diabetic population had NT-proBNP> 125 pg/mL.

Spearman correlation analyses as in Table 2 revealed a statistically significant positive correlation between serum NT-proBNP and CRP (ρ+0.576, $P<0.001$). A statistically significant positive correlation although weak existed between serum NT-proBNP and plasma FBS (ρ+0.524, $P=0.003$), plasma PPBS (ρ+0.673**, $P=0.013$), and HbA1c (ρ+0.571, $P=0.001$). A strong positive correlation also existed between serum NT-proBNP and duration of diabetes (ρ+0.780, $P<0.001$). No significant correlation

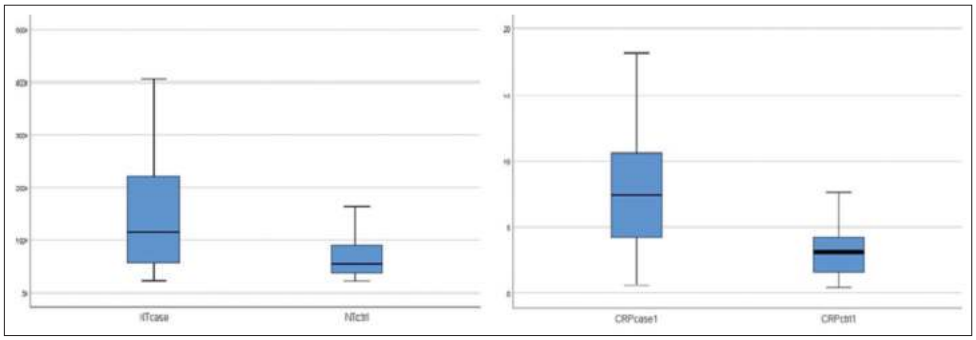

Figure 1: Box-and-whisker plot of serum NT-proBNP (pg/mL) – Cases (Median-116.5) and Control (Median-56.0) and serum C-reactive protein (mg/dL) – Cases (Median-7.4) and Control (Median-3.2)

Table 1: Comparison of serum analytes between cases and controls by Mann–Whitney U test

Analyte tested	Median (Case)	Median (Control)	Mann–Whitney U	P-value
Serum NT-proBNP (pg/mL)	116.5	56.0	1626.0	<0.001*
Serum CRP (mg/L)	7.4	3.2	1189.500	<0.001*

*P<0.05 as the significance level. NT-proBNP: N-terminal pro-B-type natriuretic peptide, CRP: C-reactive protein

Table 2: Spearman correlation analysis of blood analytes, anthropometric parameters, and duration of diabetes with serum NT-proBNP in diabetic individuals

Analytes	Rho (ρ)	P
Serum NT-proBNP: Serum CRP	+0.576	<0.001*
Serum NT-proBNP: Plasma FBS	+0.524	0.003*
Serum NT-proBNP: Plasma PPBS	+0.673	0.013*
Serum NT-proBNP: HbA1c	+0.571	0.001*
Serum NT-proBNP: WC	−0.056	0.617
Serum NT-proBNP: BMI	−0.105	0.349
Serum NT-proBNP: Duration of diabetes	+0.780*	<0.001*

*P<0.05 as the significance level. NT-proBNP: N-terminal pro-B-type natriuretic peptide, CRP: C-reactive protein, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1c: Hemoglobin A1c, WC: Waist circumference, BMI: Body mass index

was revealed between serum NT-proBNP and BMI or WC although the correlation was negative for both.

DISCUSSION

The current study revealed that diabetic subjects had a statistically significant high level of serum NT-proBNP compared to non-diabetic subjects which is similar to the study conducted by Bhandari et al.[12] The study conducted revealed that patients of T2DM have a significantly higher value of NT-proBNP. Magnusson et al. of Sweden in their study concluded that the secretion of NT-proBNP is increased in type 2 diabetic patients with no overt heart disease, suggesting that type 2 diabetes is associated with a higher prevalence of asymptomatic left ventricular.[13] In studies, diabetic patients have been concluded to have increased left ventricular mass independent of blood pressure.[17] The predominant source of energy for cardiac myocytes is fatty acid oxidation. In DM, glucose utilization is suppressed and fatty acid catabolism is enhanced which results in diabetes-associated alterations in fatty acid oxidation within cardiac myocytes leading to cardiac dysfunction.[18]

Hyperglycemia in diabetes may induce cardiac cells to secrete cytokine which promotes the recruitment of lymphocytes and monocytes that may contribute to a chronic inflammatory state and activate signaling pathways leading to cardiac hypertrophy.[19,20] This explains statistically significant high levels of CRP as found in the present study in diabetic subjects compared to non-diabetic subjects. High levels of glucose and free fatty acids activate toll-like receptor (TLR) 2 and TLR4 present in cardiomyocytes which increase leukocyte infiltration and increase nuclear factor κ-light-chain-enhancer of activated B-cell signaling.[21] This substantiates the finding of a statistically significant positive correlation of NT-proBNP and CRP in the present study. Although a retrospective study done by Van Wezenbeek of the United States of America shows no definite correlation between NT-proBNP and CRP, individually they are related to HF.[22]

In the current study, we found a positive correlation of serum NT-proBNP with the duration of diabetes in accordance with an Indian study. Longer duration of diabetes precipitates vascular complications leading to cardiac dysfunction. In a study, it was suggested patients of longer duration of diabetes must be closely monitored for HF by measuring NT-proBNP at a regular basis.[12]

In the present study, we found a statistically significant positive correlation of NT-proBNP with fasting blood sugar, postprandial blood sugar, and HbA1c similar to a study done particularly in HF patients;[12] another study suggested that 44% of patients hospitalized for HF have DM.[4] Hyperglycemic state has been shown to be responsible for increased vascular complication and HF in patients of T2DM.[12] Aguilar et al. in their study concluded that the association between HbA1c and mortality in DM patients with HF appears to be U-shaped and the lowest risk of death is in patients with HbA1c levels of ≈7.1%.[23] Some studies suggest that DM is independently associated with a greater risk of rehospitalization and death compared with non-diabetics with HF.[24] Moreover, observational data suggest that higher HbA1c level was associated with increased incidence of HF.[25] Thus, these studies confirm that significantly elevated HbA1c is associated with an increased risk of HF in the diabetic population, but an important question remains to be probed whether improved glycemic control leads to better HF outcomes in the studied population.

In the present study, no statistically significant correlation was found between serum NT-proBNP and BMI or WC although the correlation was negative. In a study conducted by Stefano Baldassare and others in the population-based Casale Monferrato Study, they found that NT-proBNP levels were significantly lower in overweight/obese compared to normal weight individuals, even in those with diabetes.[7] Another study done by Manh et al. from Hong

Kong showed a similar inverse association of NT-proBNP and BMI.[26] Epidemiological studies have researched that obese individuals, despite having left ventricular hypertrophy and higher prevalence of hypertension, have lower plasma levels of natriuretic peptides with beneficial actions on cardiac remodeling than those with normal weight.[27] In the CASA study, the inverse relationship of NT-proBNP with BMI reflected a "natriuretic handicap" in obese subjects as there is reduced response to cardiac wall stress causing progressive cardiovascular dysfunctions and ultimately HF.[7,28] Therefore, for assessing the risk of developing HF in obese individuals, lower threshold values of plasma NT-proBNP may be applicable than in normal-weight individuals as proposed in several studies.[29]

Limitations of the study

The current study had some limitations. First, a larger sample size was necessary to establish a stronger statistical outcome. Second, high-sensitivity CRP would be a better analyte than CRP which was not accessible during the study period. Moreover, this is a cross-sectional study which needs further prospective studies to study the cardiovascular outcomes in diabetic subjects and establish a relationship between NT-proBNP levels and early HF in diabetic patients. Despite these limitations, the results of the current study have identified serum NT-proBNP as a strong risk predictor of developing HF in diabetic subjects related to their glycemic and inflammatory status. In a nutshell, the measurement of serum NT-proBNP might be a simple screening test to identify diabetic patients at risk for ventricular dysfunction and early onset of HF.

CONCLUSION

The present study reveals that NT-proBNP and CRP are significantly raised in diabetic individuals as compared to non-diabetics in a population from eastern India. The study also shows a positive association of NT-proBNP with CRP, an inflammatory marker and fasting blood sugar, postprandial blood sugar, HBA1c which all indicate the glycemic status in diabetic subjects. Moreover, it also shows a strong positive correlation with the duration of diabetes. Further prospective studies with a large sample size need to be undertaken to establish a relationship between NT-proBNP and obesity in the current population. Hence, measuring serum NT-proBNP may help in the earlier identification of impending HF in diabetic individuals which will help in prompt intervention.

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REFERENCES

1. Magliano DJ, Boyko EJ and IDF Diabetes Atlas 10th edition Scientific Committee. IDF DIABETES ATLAS. 10th ed. Brussels: International Diabetes Federation; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK581934 [Last accessed on 2024 Apr 21].
2. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther. 2008;88(11):1322-1335.
https://doi.org/10.2522/ptj.20080008
3. Steiner G. Diabetes and atherosclerosis: An overview. Diabetes. 1981;30(Suppl 2):1-7.
https://doi.org/10.2337/diab.30.2.s1
4. Echouffo-Tcheugui JB, Xu H, DeVore AD, Schulte PJ, Butler J, Yancy CW, et al. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: Findings from get with the guidelines-heart failure registry. Am Heart J. 2016;182:9-20.
https://doi.org/10.1016/j.ahj.2016.07.025
5. Kannel WB and McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979;241(19):2035-2038.
https://doi.org/10.1001/jama.241.19.2035
6. Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, et al. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. Circulation. 2001;103(1):102-107.
https://doi.org/10.1161/01.cir.103.1.102
7. Baldassarre S, Fragapani S, Panero A, Fedele D, Pinach S, Lucchiari M, et al. NTproBNP in insulin-resistance mediated conditions: Overweight/obesity, metabolic syndrome and diabetes. The population-based Casale Monferrato Study. Cardiovasc Diabetol. 2017;16(1):119.
https://doi.org/10.1186/s12933-017-0601-z
8. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JG, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019;21(6):715-731.
https://doi.org/10.1002/ejhf.1494
9. Richards AM. N-terminal B-type natriuretic peptide in heart failure. Heart Fail Clin. 2018;14(1):27-39.
https://doi.org/10.1016/j.hfc.2017.08.004
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, 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 J Heart Fail. 2016;18(8):891-975.
https://doi.org/10.1002/ejhf.592
11. Maisel AS, Duran JM and Wettersten N. Natriuretic peptides in heart failure: Atrial and B-type natriuretic peptides. Heart Fail Clin. 2018;14(1):13-25.
https://doi.org/10.1016/j.hfc.2017.08.002
12. Bhandari S, Rankawat G, Agarwal A and Gupta V. A comparative

study of plasma N-terminal Pro- brain natriuretic peptide to assess asymptomatic cardiovascular disease in type 2 diabetic patients. Austin J Endocrinol Diabetes. 2023;10(1):1098.

13. Magnusson M, Melander O, Israelsson B, Grubb A, Groop L and Jovinge S. Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. Diabetes Care. 2004;27(8):1929-1935.
https://doi.org/10.2337/diacare.27.8.1929
14. Birukov A, Eichelmann F, Kuxhaus O, Polemiti E, Fritsche A, Wirth J, et al. Opposing associations of NT-proBNP with risks of diabetes and diabetes-related complications. Diabetes Care. 2020;43(12):2930-2937.
https://doi.org/10.2337/dc20-0553
15. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S17-S38.
https://doi.org/10.2337/dc22-s002
16. Cazzoletti L, Zanolin ME, Dorelli G, Ferrari P, Dalle Carbonare LG, Crisafulli E, et al. Six-minute walk distance in healthy subjects: Reference standards from a general population sample. Respir Res. 2022;23(1):83.
https://doi.org/10.1186/s12931-022-02003-y
17. Chuang SM, Liu SC, Leung CH, Lee YT and Chien KL. High left ventricular mass associated with increased risk of incident diabetes. Sci Rep. 2024;14(1):250.
https://doi.org/10.1038/s41598-023-50845-3
18. Schulze PC, Drosatos K and Goldberg IJ. Lipid use and misuse by the heart. Circ Res. 2016;118(11):1736-1751.
https://doi.org/10.1161/circresaha.116.306842
19. Scherer PE and Hill JA. Obesity, diabetes, and cardiovascular diseases: A compendium. Circ Res. 2016;118(11):1703-1705.
https://doi.org/10.1161/circresaha.116.308999
20. Kenny HC and Abel ED. Heart failure in type 2 diabetes mellitus. Circ Res. 2019;124(1):121-141.
https://doi.org/10.1161/circresaha.118.311371
21. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H and Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest. 2006;116(11):3015-3025.
https://doi.org/10.1172/jci28898
22. Van Wezenbeek J, Canada JM, Ravindra K, Carbone S, Trankle CR, Kadariya D, et al. C-Reactive protein and N-terminal pro-brain natriuretic peptide levels correlate with impaired cardiorespiratory fitness in patients with heart failure across a wide range of ejection fraction. Front Cardiovasc Med. 2018;5:178.
https://doi.org/10.3389/fcvm.2018.00178
23. Aguilar D, Bozkurt B, Ramasubbu K and Deswal A. Relationship of hemoglobin A1C and mortality in heart failure patients with diabetes. J Am Coll Cardiol. 2009;54(5):422-428
https://doi.org/10.1016/j.jacc.2009.04.049
24. Echouffo-Tcheugui JB, Masoudi FA, Bao H, Spatz ES and Fonarow GC. Diabetes mellitus and outcomes of cardiac resynchronization with implantable cardioverter-defibrillator therapy in older patients with heart failure. Circ Arrhythm Electrophysiol. 2016;9(8):e004132.
https://doi.org/10.1161/circep.116.004132
25. Erqou S, Lee CT, Suffoletto M, Echouffo-Tcheugui JB, de Boer RA, van Melle JP, et al. Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: Systematic review and meta-analysis. Eur J Heart Fail. 2013;15(2):185-193.
https://doi.org/10.1093/eurjhf/hfs156
26. Ha Manh T, Do Anh D and Le Viet T. Effect of body mass index on N-terminal pro-brain natriuretic peptide values in patients with heart failure. Egypt Heart J. 2023;75(1):75.
https://doi.org/10.1186/s43044-023-00401-1
27. Sugisawa T, Kishimoto I, Kokubo Y, Makino H, Miyamoto Y and Yoshimasa Y. Association of plasma B-type natriuretic peptide levels with obesity in a general urban Japanese population: The Suita study. Endocr J. 2010;57(8):727-733.
https://doi.org/10.1507/endocrj.k10e-067
28. Ricci MA, De Vuono S, Pucci G, Di Filippo F, Berisha S, Gentili A, et al. Determinants of low levels of brain natriuretic peptide in morbid obesity. Clin Nutr. 2017;36(4):1075-1081.
https://doi.org/10.1016/j.clnu.2016.06.024
29. Ndumele CE, Matsushita K, Sang Y, Lazo M, Agarwal SK, Nambi V, et al. N-terminal pro-brain natriuretic peptide and heart failure risk among individuals with and without obesity: The atherosclerosis risk in communities (ARIC) study. Circulation. 2016;133(7):631-638.
https://doi.org/10.1161/circulationaha.115.017298

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SD- Concepts, literature survey, implementation of study protocol, data collection, investigation, statistical analysis, manuscript writing; **SB-** Concepts, design, definition of intellectual content; **MS-** Design, statistical analysis, literature survey, manuscript writing, article submission.

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