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NT- proBNP: Linking Cardiovascular and Microvascular Diabetes Complications

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ABSTRACT

Background: NT-proBNP is an established biomarker of myocardial stress and heart failure. Recent evidence suggests its association with both cardiovascular and microvascular complications in diabetes.

Objective: To provide an updated narrative review integrating recent guidelines of the American Diabetes Association (ADA), contemporary literature, and our previously published research clinical data. The review aims to confirm the relationship between NT-proBNP and cardiac complications, including subclinical heart failure, and the degree of microvascular renal and retinal complications.

Methods: We wrote a narrative review drawing on the ADA Standards of Care (2026), major international cohort studies, and previously published data from our own study.

Results: Elevated NT-proBNP is associated with increased subclinical cardiovascular risk and higher prevalence of diabetic retinopathy, neuropathy, and progressive nephropathy and retinopathy.

Conclusion: NT-proBNP may serve as an integrative biomarker for subclinical cardiovascular and microvascular risk stratification in diabetes.

Keywords: NT-proBNP; Diabetes Mellitus; Cardiovascular Complications; Microvascular Complications; Heart Failure; Biomarkers; Risk Stratification

Introduction

Diabetes mellitus is a leading cause of cardiovascular morbidity and mortality worldwide, with cardiovascular disease remaining the principal cause of death among individuals with diabetes[1]. Heart failure frequently develops silently in patients with diabetes, often preceding overt clinical symptoms and resulting in delayed diagnosis and treatment[2]. The American Diabetes Association (ADA) recommends considering natriuretic peptide testing, including B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), to facilitate early detection of subclinical cardiac dysfunction in high-risk individuals[3].

NT-proBNP- the inactive amino-terminal fragment- together with the biologically active BNP, are 2 cleavage products of the precursor pre-pro BNP, which is formed in ventricular myocytes in response to physiological signals. These signals can be stretching of the ventricular wall or changes in systemic blood pressure, sodium levels, or extracellular volume. The B-type natriuretic peptide is broken down after binding to its specific natriuretic peptide receptors. Its receptors are found in the kidney, lung, liver, and along the vascular endothelium. At the same time, NT-proBNP is cleared primarily by the kidneys and has currently been known as a new useful biochemical marker to either diagnose or exclude congestive heart failure (CHF)[4].

B- type Natriuretic Peptide and Early Heart Disease in Diabetes

The American Diabetes Association publishes annually updated Standards of Care in Diabetes. In the 2026 edition, expanded recommendations address heart failure risk assessment in individuals with diabetes, emphasizing the importance of early identification of asymptomatic structural and functional cardiac disease through measuring either BNP or NT pro-BNP and doing echocardiography if any of them is found to be abnormal[5].

Patients with diabetes are predisposed to diabetic cardiomyopathy, left ventricular hypertrophy, diastolic dysfunction, and myocardial fibrosis because of chronic metabolic derangements, endothelial dysfunction, and low-grade inflammation. These abnormalities frequently precede clinical manifestations and correspond to stage B heart failure[6]. Accordingly, clinicians are advised to consider measurement of BNP or NT-proBNP in adults with long-standing diabetes, hypertension, chronic kidney disease, or established microvascular complications.

Elevated natriuretic peptide levels indicate an increased likelihood of left ventricular dysfunction, future heart failure, cardiovascular hospitalization, and mortality[7]. Patients with abnormal values should therefore undergo echocardiographic evaluation and intensified cardiovascular risk management[8].

In patients with diabetes, increased plasma levels of NT-proBNP are a strong predictor of cardiovascular and all-cause mortality, even in people with no pre-existing clinical cardiovascular disease[9]. Furthermore, the increased plasma level of pro BNP has been related to coronary heart disease in patients with type 2 diabetes[10]. BNP screening has been suggested to diagnose subclinical cardiomyopathy due to diabetes. Moreover, normal proBNP showed a very high negative predictive value to exclude the intermediate risk of cardiovascular events[8].

Recent prospective and cross-sectional studies have strengthened the evidence linking NT-proBNP to diabetic cardiovascular and microvascular complications. Pop-Busui et al. demonstrated that elevated NT-proBNP predicted incident heart failure and all-cause mortality in individuals with diabetes without known heart failure[11]. Also, Landolfo et al. showed that NT-proBNP identifies subclinical heart stress in asymptomatic patients with type 2 diabetes[12].

Tiwari & Aw review the increasing clinical significance of BNP and NT-proBNP as biomarkers for diagnosing, risk-stratifying, and managing cardiovascular complications, particularly heart failure (HF), in individuals with type 2 diabetes mellitus. Their

paper highlights how elevated natriuretic peptides (NPs) indicate cardiac stress in diabetic patients. The review suggests using NPs to guide therapeutic strategies, particularly with newer pharmacological agents, such as neprilysin inhibitors, that affect NP levels[13].

Joshi et al, from India, highlighted the screening of patients with type 2 diabetes mellitus attending the diabetes clinic by measuring NT- proBNP to diagnose stage B heart failure[14].

B-type Natriuretic Peptide and Diabetic Microvascular Complications: Real-world Data

Although the ADA does not formally recommend NT-proBNP for routine microvascular screening, it recognizes that microvascular disease reflects systemic vascular injury and is closely linked to cardiovascular risk [15]. This overlap provides a strong rationale for investigating NT-proBNP as an integrated biomarker of global vascular dysfunction in patients with diabetes.

Large international cohort studies support this concept. The ADVANCE trial demonstrated that higher NT-proBNP levels were associated with increased risk of microvascular events, renal impairment, and cardiovascular mortality. Data from the ADVANCE study, which included patients with type 2 diabetes, showed that microvascular complications were more related to higher means of NT- proBNP. Patients with nephropathy showed a significantly higher mean BNP of 149 pg/mL, while those without nephropathy showed a mean BNP of 78 pg/mL, with a p-value <0.01. When comparing patients with retinopathy to those without retinopathy, there was no significant difference in the mean proBNP level. However, there was a log-linear association between BNP and microvascular outcomes (P values <0.001)[16].

On the other hand, the EURODIAB study reported independent associations with nephropathy, retinopathy, and neuropathy. Data from the EURODIAB study, which tackled patients with type 1 diabetes, with its regression analysis model adjusted for age, sex, and diabetes duration (model 1), showed that subjects with the lowest NT-proBNP quartiles (NT-proBNP<26.46 pg/ml), had significantly decreased ORs (odds ratios) for nephropathy and neuropathy but not retinopathy when compared to those in the highest quartiles (NT-proBNP>84.71 pg/ml)[17]. However, the odds ratios for retinopathy showed statistical significance (2.18 [95% CI 1.03–4.60]) only after further adjustment for body mass index (BMI). In (model 2), full adjustment was performed for main risk factors (BMI, HbA1c, hypertension, LDL cholesterol, albumin excretion rate, and smoking) and potential confounders (eGFR and ECG-LVH (left ventricular hypertrophy)). Only with full adjustment (model 2), higher NT proBNP quartiles were associated with significantly increased ORs for all 3 parameters: nephropathy, retinopathy, and neuropathy[17].

A Japanese study by Seki and colleagues, which targeted patients with type 2 diabetes mellitus, showed that the BNP level has a positive correlation with diabetic nephropathy, and a low BNP level can predict remission of diabetic nephropathy[18]. In an update of the same study, they postulated that the higher the BNP level, the higher the degree of diabetic nephropathy is, and BNP predicts the prognosis as well[19]. The same finding was confirmed by Yasuda et al.[20].

Chaturvedi et al. reported differences in serum proBNP related to diabetic retinopathy grades, with significant correlations with OCT and OCT-angiography measures[21]. Zhao et al. also showed that NT-proBNP correlated with proteinuria, renal histopathology, and independently predicted progression to end-stage kidney disease[22]. On the other side, Ma et al. demonstrated that NT-proBNP can be used in cardiorenal risk prediction[23].

Other data from around the world highlighted a similar relation of NT-proBNP and microvascular complications of diabetes. Diabetic retinopathy was related to higher cardiovascular and all-cause mortality risk in both type 1 and type 2 diabetes

mellitus[24]. Several reports proved the interrelation of diabetic microangiopathy with macroangiopathy; hence, diabetic retinopathy has been suggested as a cardiovascular risk stratification marker[25]. Similarly, microalbuminuria has been established not only as a marker for the risk of microvascular complications but also as a predictor of cardiovascular disease[26]. Studies showed an association between NT-proBNP and diabetic complications in a large group of type 1 diabetes patients. Other reports also proposed that high levels of proBNP can be used as markers of incipient microvascular complications, including retinopathy[27] and nephropathy[28].

Data from Our Original Research

In a previously published cross-sectional study in 2023 that studied 236 Emirati adults with type 2 diabetes attending the diabetes and endocrinology clinic, we studied the relation of NT-proBNP with microvascular complications. Patients were stratified according to NT-proBNP levels using a threshold of 100 pg/mL. Individuals with elevated NT-proBNP demonstrated significantly higher prevalence of diabetic retinopathy and neuropathy[29].

The odds ratio for retinopathy was 2.196 (95% CI: 1.307–3.689, p=0.003), and for neuropathy was 1.607 (95% CI: 1.046–2.469, p=0.031), respectively, in patients with NT-proBNP≥ 100. Progressive increases in retinopathy and albuminuria severity were observed with a corresponding increase in NT- proBNP[29].

After adjustment for age, sex, body weight, and HbA1c, NT-proBNP remained significantly associated with retinopathy and showed an almost significant relation with neuropathy[29].

Role of Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i) and Glucagon-Like Peptide Receptor Agonists (GLP1RA):

ADA guidelines highlighted the role of SGLT2i and GLP1RA with demonstrated cardiovascular benefit as essential medications for patients with type 2 diabetes mellitus to decrease the risk of cardiovascular and renal complications.[5] They advised prescribing SGLT2i for patients with heart failure with or without preserved ejection fraction to decrease the progression[5] of heart failure and cardiovascular death. ADA also advised that patients with type 2 diabetes mellitus with stage B heart failure or cardiovascular risk should be on an SGLT2i or GLP1RA with heart failure prevention benefit to avoid the risk of hospitalization due to heart failure[5]. ADA also advised using these two groups of medications for patients with chronic kidney disease[5].

A study by Ching et al. shows that SGLT2i use was associated with a lower incidence of cardiovascular disease, major microvascular complications, and mortality than DPP-4 inhibitors, sulfonylureas, and GLP-1RA in patients with type 2 diabetes without prior macrovascular or microvascular disease. They recommended using SGLT2i for primary prevention[30]. Another meta-analysis by Tsampasian et al. shows that SGLT2i use favoured the prognosis of patients with heart failure, regardless of the exact mechanism of action, in patients with or without diabetes. The results of this study also suggest that SGLT2i are likely more effective in patients with reduced ejection fraction[31]. On the other hand, a meta- analysis done by Dorsey-Trevino et al. using data from a total of 40 randomized controlled trials showed that SGLT-2i reduced the risk of renal-replacement therapy (0.65; 95% CI 0.54–0.79), death due to a renal disease (0.57; 95% CI 0.49–0.65), and progression of albuminuria (0.69; 95% CI 0.66–0.73)[32].

Conclusion

Integration of NT-proBNP measurement into routine diabetes care may facilitate early identification of patients at high cardiovascular and microvascular risk. Such patients may benefit from early cardioprotective therapy (including SGLT2i and GLP-1RA), intensified risk factor control, and closer surveillance.

Higher NT-proBNP reflects broader vascular injury, including retinal, renal, and neural microangiopathy, supporting its role as an integrative biomarker in diabetes care.

Ethics and Transparency Statement:

Parts of this manuscript build upon previously published data. The current article represents a substantially expanded synthesis integrating updated guidelines and contemporary literature. All original data were collected following ethical approval and informed consent.

Conflict of Interest:

The author declares no conflicts of interest.

Author Contributions:

Dr. Pierre Samir Mosaad Raoof conceived the study, conducted the literature review, analysed the data, and prepared the manuscript.

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