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Review Article

BNP AND NT-PRO BNP AS INDEPENDENT DIAGNOSTIC BIOMARKERS FOR CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

The risk of developing heart failure (HF) with a reduced and preserved ejection fraction is known to increase with pre-diabetes and diabetic mellitus (DM). Natriuretic peptides (NPs) have been shown to be an important tool for assessing the risk of cardiovascular diseases (CVD) in people with pre-diabetes and Type 2 diabetes (T2DM), regardless of HF characteristics. Elevated levels of NPs were associated with an increased risk of readmission for HF, all-cause mortality, CVD mortality, HF progression, and readmission due to HF, according to earlier clinical investigations. In pre-diabetes and T2DM populations, the discriminative power of NPs for CVD death and HF-related clinical events has not been established beyond conventional CVD risk variables. The purpose of the review is to gather details regarding the predictive value of circulating NPs based on pre-diabetes and established T2DM presentation. Researchers have found that HFrEF or HFpEF in T2DM patients may necessitate a change in NP cutoff values to diagnose primary HF and identify HF-related risks. The relationship between clinical outcomes and the dynamic of circulating levels of NPs in diabetics treated with glucagon-like peptide-1 agonists and sodium-glucose cotransporter-2 inhibitors has to be clarified in big clinical trials in the future.

Keywords: T2DM, CVD, Biomarker, BNP, NT-proBNP.

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BACKGROUND

Biomarkers have become crucial diagnostic, risk-based, and therapeutic decision-making tools for cardiovascular illnesses in recent years [1,2]. Particularly, cardiac troponins have become the cornerstone of the diagnostic process for patients with acute coronary syndromes. The scientific community is currently studying a number of intriguing novel biomarkers. Except for B-type natriuretic peptide (BNP) and its N-terminal fragment, most of these novel biomarkers are not yet appropriate for therapeutic use (NT-proBNP) [3]. Both markers have advanced from the laboratory bench to clinical application as a result of numerous research demonstrating their diagnostic value. The goal of the present studies is to provide a comprehensive review of the literature on BNP and NT-proBNP measurements in Type 2 diabetic mellitus (T2DM) patients with cardiovascular disease (CVD) and their therapeutic implications [4].

PHYSIOLOGY OF BNP AND NT-PROBNP

BNP, also known as brain-type natriuretic peptide, was isolated from pig brain in 1988 and was originally characterized in same year. However, it was quickly discovered that it is mostly a cardiac hormone that comes from the heart. The natriuretic peptide family includes BNP and additional peptides including atrial natriuretic peptide, C-type natriuretic peptide, and urodilatin that have structurally similar features [5]. A ring of 17 amino acids and a disulfide bridge connecting two cysteine molecules make up the comparable and distinctive structural structure of the natriuretic peptides. The primary site of BNP synthesis and secretion is the ventricular myocardium. Only little amounts of BNP are stored in granules, and the process controlling BNP secretion relies on rapid gene expression and *de novo* peptide synthesis. Atrial natriuretic peptide, in contrast, is kept in granules and can be released immediately after stimulation. BNP, a prohormone made up of 108 amino acids, is produced (proBNP) [6]. On release into circulation, ProBNP is cleaved in equal proportions into the biologically inactive 76 amino acid N-terminal fragment and the physiologically active 32 amino acid BNP, which is the C-terminal fragment (NT-proBNP) [7]. Both molecules are continuously released and are visible in blood. Myocardial wall stress is the primary trigger for increased BNP and NT-proBNP production and secretion. In addition, elements like myocardial ischemia and endocrine and paracrine regulation by other neurohormones and cytokines, respectively, are significant [4,7].

Numerous biological processes in systemic circulation are mediated by the interaction between BNP and the natriuretic peptide receptor Type A, which leads to the production of intracellular cyclic GMP. BNP has a number of physiological effects, including natriuresis, diuresis, peripheral vasodilation, and inhibition of the sympathetic nervous system and renin-angiotensin-aldosterone system. BNP is taken out of the plasma by binding to natriuretic peptide receptor Type C and being proteolyzed by neutral endopeptidases [8]. The main mode of NT-proBNP clearance, however, is renal excretion. The idea that NT-proBNP might be eliminated through more important pathways is raised by recent studies, nevertheless. Although both molecules are released in equimolar proportions, NT-proBNP serum levels are around 6 times higher than BNP levels. This difference can be attributed to NT-proBNP, which has a half-life of 120 min as opposed to BNP's 20 min [4,9].

TYPE 2 DIABETES MELLITUS WITH CARDIOVASCULAR DISEASE

The most prevalent metabolic illness in the world, DM, is the eighth greatest cause of mortality [5]. According to DM data, 500 million people worldwide will have the condition by 2030 [10]. In 2013, 382 million people worldwide were estimated to have it. The Reduction of Atherothrombosis for Continued Health registry found that people with T2DM had a higher risk of cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke compared to those without T2DM [11]. Thus, T2DM was independently associated with a 33% increased risk of heart failure (HF), HF-related events, and CVD death [12,13]. In addition, T2DM and CVD illnesses frequently coexist, and CVD risk factors have a considerable impact on both conditions' onset

and progression [14]. Although some anti-diabetic drugs have an impact on CVD risk factors, there is not a perfect correlation between reducing the risk of T2DM-related outcomes and CVD complications and controlling for traditional CVD risk variables such glycemic state by lifestyle changes and medication [15-17]. In addition, non-T2DM patients with known CVD illness may have an even higher mortality risk than T2DM patients without established CVD [17]. In this situation, it is necessary to individually modify the advanced risk stratification technique for patients with pre-diabetes and known T2DM using the biomarker prediction scores [18]. Among the many circulating biomarkers and numerous biomarker-based models reflecting various pathophysiological stages of the development of both T2DM and HF, natriuretic peptides (NPs) continue to be a crucial part of the strategy for assessing CVD risk and a molecular target for guided therapy of HF [19]. The severe variability of circulating levels in patients with metabolic diseases, such as abdominal obesity, metabolic syndrome, and T2DM, necessitates the modification of the diagnostic and predictive cutoff points for NPs, despite the fact that NPs continue to be a helpful biomarker for the diagnosis of HF and the prediction of all-cause mortality, CVD death, and HF. The purpose of the brief review is to compile the latest information on the debatable prognostic function of circulating BNP and NT-proBNP in patients with pre-diabetes and developed T2DM.

CLINICAL APPLICATIONS OF NT-proBNP

The main population in which studies on the diagnostic value of BNP and NT-proBNP have been conducted is HF patients. According to functional class (New York Heart Association), left ventricular systolic ejection fraction, and left ventricular diastolic function, the levels of BNP and NT-proBNP have also been discovered to be connected to the severity of the condition [5]. It has been consistently found that patients with HF have elevated levels of BNP and NT-proBNP. High BNP and NT-proBNP levels in patients with HF or asymptomatic left ventricular dysfunction strongly predict an adverse outcome regardless of their diagnostic value, according to several large-scale studies [10,11]. BNP and NT-proBNP were found to perform better in multivariable models than other prognostic measures, and in several studies, they were the sole independent prognostic factors. Both HF patients and patients with asymptomatic left ventricular failure have been the subjects of studies comparing the diagnostic potency of BNP and NT-proBNP tests. These tests showed that both markers performed equally well, with approximately identical areas under the receiver operating characteristic curves [11,20]. Therefore, it may be inferred from these studies that there is no appreciable distinction between the markers in terms of clinical routine risk categorization.

CONCLUSIONS

Excellent biomarkers for a lot of cardiovascular illnesses include NT-proBNP and BNP. By using tests that are sold for this purpose, both markers can be identified in serum plasma. When comparing the diagnostic performance of NT-proBNP with BNP, there is no discernible difference. They depict hemodynamic myocardial stress independent of the underlying illness, making them generic for CVD rather than specialized for a particular pathology like HF. When patients visit the emergency room complaining of shortness of breath, they are excellent at ruling out HF. They provide trustworthy and unbiased prognostic information to patients with HF, stable coronary artery disease, acute coronary syndromes, and valvular aortic stenosis. However, there are currently no data to support the use of these markers in patients with CVD for making therapy decisions. There is some evidence that suggests BNP and NT-proBNP measurements may aid in choosing the most appropriate course of treatment for HF patients.

CONFLICT OF INTEREST

Nil.

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