

Emerging diagnostic and predictive utilities of natriuretic peptides in diabetes mellitus patients at high cardiovascular risk

Alexander E Berezin^{1*} and Alexander A Berezin²

¹Internal Medicine Department, State Medical University, Ministry of Health of Ukraine, Zaporozhye, 69035, Ukraine

²Internal Medicine Department, Medical Academy of Post-Graduate Education, Ministry of Health of Ukraine, Ukraine²University of Rio Verde, UniRV, Medical School, Rio Verde, GO, Brazil

Abstract

Pre-diabetes and diabetes mellitus (DM) are established cardiovascular (CV) risk factors, which contribute to heart failure (HF) with reduced (HF_rEF) and preserved (HF_pEF) ejection fraction. Natriuretic peptides (NPs) were found to be useful tool for CV risk stratification among patients with pre-diabetes and T2DM regardless of HF. Previous clinical studies have shown that elevated levels of NPs predicted all-cause and CV mortality, risk of HF manifestation and progression, as well as risk re-admission due to HF. The discriminative potency of NPs for CV death and HF-related events in pre-diabetes and T2DM populations has not been demonstrated beyond traditional CV risk factors. The aim of the review is to accumulate knowledge regarding differential prognostic role of circulating NPs in patients with pre-diabetes and established T2DM. Presences of HF_rEF or HF_pEF in T2DM patients may require modification of NP cut-off points to primary diagnose HF and determine HF-related risks. There are several controversies between clinical outcomes and dynamic of circulating levels of NPs in diabetics treated with glucagon-like peptide-1 agonists and sodium-glucose co-transporter-2 inhibitors that requires to be elucidated in large clinical studies in the future.

Introduction

Diabetes mellitus (DM) has reached epidemic level and nowadays became the most common metabolic disorders worldwide occupying the 8th leading cause of death [1]. The global statistics of DM has yielded about 382 million people had this disease in 2013 worldwide and by 2030 the number of diabetics will have reached 500 million people [2]. According to the REACH (Reduction of Atherothrombosis for Continued Health) registry patients with type 2 DM (T2DM) compared with patients without DM had higher risk of cardiovascular (CV) death, nonfatal myocardial infarction, or nonfatal stroke [3]. Therefore, T2DM was independently associated with a 33% greater risk of hospitalization for heart failure (HF), HF-related and CV death [4,5]. Noted, T2DM and CV diseases coexist frequently and CV risk factors influence significant impact on manifestation and progression of both conditions [6]. Although CV factors are affected by several antihyperglycemic medications, there is not complete correspondence between a control for conventional CV risk factors including glycemic status by life style modification, drug prescription and diminishing risk of T2DM-related and CV complications [7-9]. In this context, risk stratification strategy among patients with prediabetes and known T2DM requires to be personally modified and this improvement perhaps can be based on biomarker prediction scores [10]. Among numerous circulating biomarkers and multiple biomarker-based models reflecting various stages of CV disease manifestation and HF advance natriuretic peptides (NPs) continue to be a core element in CV risk assessment and targets in guided therapy of HF [11]. However, serious variability of circulating levels of NPs in patients with metabolic diseases, including abdominal obesity, metabolic syndrome and DM, due to several reasons requires an adjustment of the diagnostic and predictive cut-off levels of NPs,

while the NPs remain useful diagnostic and predictive biomarker for all-cause mortality, CV death and HF regardless of presence of HF. The aim of the mini review is to accumulate knowledge regarding differential prognostic role of circulating NPs in patients with pre-diabetes and established T2DM.

Myocardial biomechanical stress in T2DM

Previous magnetic resonance imaging studies have revealed that alterations in glucose metabolism were independently associated with left ventricular (LV) concentric remodeling, less spherical shape, and reduced systolic myocardial shortening in the general population [12-14]. Moreover, speckle-tracking echocardiography studies have yielded that myocardial shortening, LV torsion and myocardial strain was progressively decreased with higher HOMA-IR and torsion was increased only with less severe insulin resistance in individuals with prediabetes [15,16]. In the CARDIA (Coronary Artery Risk Development in Young Adults) study patients with established T2DM had lowered LV ejection fraction (LVEF), longitudinal systolic strain, and early diastolic strain rate when compared with patients having

*Correspondence to: Alexander E. Berezin, Professor, MD, PhD, Senior Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University for Zaporozhye, 26, Mayakovsky av., Zaporozhye, Postcode 69035, Ukraine, Tel: +38 061 2894585, Fax: +38 0612894585, E-mail: aeberezin@gmail.com

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normal glucose metabolism [16]. The population STAAB cohort study has demonstrated that LV global longitudinal strain and torsion were inversely associated with glycosylated hemoglobin (HbA1c) and insulin resistance and that these parameters were found significantly lowered in diabetics in compared with non-diabetics without known CV disease [17].

In fact, glucose abnormalities, lipid toxicity, altered tissue repair, accelerating atherosclerosis, and co-existing conventional CV risk factors are causes to develop diabetic cardiomyopathy as well as HF related to ischemia causes [18,19]. In fact, atherosclerosis, systemic and micro vascular inflammation, myocardial fibrosis, myocardial infarction, or LV contractile / diastolic dysfunction due to microvascular obstruction are primary reasons for myocardial remodeling, for which myocardial biomechanical stress is discussed as crucial pathogenetic mechanism leading to HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) [20]. Indeed, T2DM through several molecular mechanisms, such as renin-angiotensin system activation, cardiac autonomic neuropathy, alterations in calcium homeostasis, generation of reactive oxygen or nitrogen species leading to mitochondrial dysfunction, causes ischemic myocardial injury, which represents the major cause of death in diabetic subjects, diabetic cardiomyopathy summarizes adverse effects of T2DM on the myocardium regardless of presence of coronary artery disease (CAD) and hypertension [21]. Having evidence that conventional CV risk factors, CAD, and diabetic cardiomyopathy influence negatively on mortality rate and quality-of-life among T2DM patients, there is a suggestion that cardiac biomarkers reflecting various faces of altered cardiac remodeling and HF advance, such as natriuretic peptides, would ensure add-on incremental value for the prediction of clinical outcomes (death, MACEs, hospital admission, HF-related events) in the patient population. Moreover, the levels of natriuretic peptides, could demonstrate personifying predictive information that would be able to yield the greatest predictive potency beyond conventional CV risk factors [22].

Natriuretic peptides: biological role and function

Biological role of NPs' system as a core element in a regulation of natriuresis, vasodilation, water and sodium homeostasis are well established and wide known [23]. Indeed, predominantly atrial (ANP) and brain (BNP) and rarely C-type of NP are embedded onto a regulation of cardiorenal homeostasis through appropriate receptor A (NPRA). Clearance of NPs are mediated by their proteolysis by endogenous endopeptidase called neprilysin that activates physiological pathways by which NPs are effectively removed from circulation through receptor-mediated internalization by the NP receptor C (NPRC) [24]. In fact, both types of the NPs' receptors (NPRA and NPRC) as well as activity and circulating levels of neprilysin ensure determines the NP bioactivity [25]. The main triggers for NPs' secretion are myocardial stretching, fluid overload, ischemia / hypoxia, inflammation, and renin-angiotensin-aldosterone system (RAAS) [26]. Although system of the NPs is a physiological antagonist of RAAS, there is a wide range of evidence regarding that the NPs through adipose tissue-expressed NPRA and NPRC reciprocally regulate lipolytic activity of adipocytes similar to catecholamine-derived effect that is mediated by the β -adrenergic receptors [27]. Additionally, NPs via p38 MAP kinase act as a triggers for over-expression of brown fat genes to increase energy expenditure and regulate adaptive thermogenesis [28]. Therefore, in human cells, including adipocytes, muscle cell, hepatocytes, NPs promote transcriptional regulation of genes involved in mitochondrial biogenesis, uncoupled respiration (peroxisome proliferator-activated

receptor- γ coactivator-1 α and uncoupling protein 1), lipid oxidation, as well as glucose tolerance insulin resistance [29,30]. Overall, activation of NPRA signaling pathway in skeletal muscle and hepatocytes is crucial for the maintenance of long-term insulin sensitivity and this phenomenon can link transformation of pre-diabetes to T2DM as well as ensures rockets of CV risk [31,32].

Natriuretic peptides in pre-diabetes and T2DM

Previous studies have shown that patients with abdominal obesity, metabolic syndrome, and T2DM may have rather lower levels of NPs than healthy volunteers and that this effect relates to clearance of NPs especially activity of neprilysin [33,34]. Indeed, insulin may up-regulate the NPRC expression in the subcutaneous fat depot in obese individuals [35], while the difference between healthy volunteers and obese patients in the circulating levels of NPs was not confirmed by several investigators [36,37]. Therefore, kidney clearance of NPs was found to be worse in T2DM with nephropathy that was associated with increased circulating levels of BNP and NT-pro-BNP [38]. However, the reasons for NP level fluctuation in patients with metabolic disease remain still uncertain.

Natriuretic peptides in HF associated with abnormalities of glucose status

Current clinical guidelines recommend using biomarker level measure to diagnose HF when diagnosis is uncertain, stratify patients from general population into group with higher risk of CV mortality rate and HF manifestation, as well as to prognosticate risks of HF advance and 60-day re-admission regardless of presentation of abdominal obesity, pre-diabetes, and T2DM [39,40]. However, asymptomatic patients from general population to be stratified at a risk of death and HF onset should have higher circulating levels of NT-proBNP (>300 pg/mL) than individuals having signs and symptoms of HF (125 pg/mL) [40]. In fact, increased age requires re-checking diagnostic NT-proBNP cut-off point for patients suspecting cardiac dysfunction [38,41]. Interestingly, among patients without T2DM, elevated levels of NPs yielded greater predictive accuracy for CAD, MACEs, CV mortality and HF manifestation than in T2DM patients [39,42]. Although the circulation levels of NT-proBNP were not differ between male and female in general population, elevated NT-proBNP concentrations rather conferred a higher risk of CV mortality in women with HFpEF than in male with HFpEF [43]. However, T2DM patients have demonstrated more LV hypertrophy and adverse cardiac remodeling, but systolic and diastolic LV function parameters as well as NT-proBNP serum levels were found to be similar in T2DM and non-T2DM patients [44]. Therefore, in patients with abdominal obesity, metabolic syndrome and T2DM serum levels of NPs were found to be independent predictors for atherosclerosis, albuminuria, atrial fibrillation, pulmonary hypertension, and sudden death rate, but in patient population with HFrEF predictive value of NPs for these outcomes was not related to presentation of prediabetes and T2DM [45-47]. Despite NT-proBNP levels were lower in overweight/obesity patients, even in those with T2DM, but higher than in healthy volunteers, NT-proBNP level may have predictive value to diagnose cardiac abnormalities regardless of glucose status [48]. Moreover, multiple biomarkers' models including NP levels occurred to be more prognostically accurate for HF onset in non-T2DM patients that in pre-diabetics with abdominal obesity and T2DM patients [49,50].

There are several controversies regarding predictive abilities of elevated levels of NPs in patients with metabolically healthy obesity and metabolic syndrome. First controversy was related to evidence that NPs

were not better than conventional cardiac biomarkers, such as cardiac troponins, soluble ST2, ischemia-modified albumin in prediction of the onset of future microvascular and macrovascular complications in obese/ prediabetes patients without known CV disease [51]. In contrast, metabolic biomarkers (adiponectin, chemerin, visfatin) sufficiently increased predictive value of NT-proBNP levels for MACEs in patients with various glucose statuses and established HF [52-54]. The next controversy affects negative associations between NPs' serum levels (including ANP, NT-proANP, NT-proBNP) and several components of the metabolic syndrome in young people without CV disease, while the inverse relationships between several components of the metabolic syndrome and circulating NP concentrations were found in middle-aged and elderly populations [55]. Finally, elevated levels of NT-proBNP remain strong predictor of death in patients with established CV diseases including CAD and HF, even with the confounding effect of pre-diabetes and T2DM [56], but it is still uncertain whether the discriminative potency of NPs for CV death and events in prediabetes and T2DM populations beyond CV disease would be independent from traditional CV risk factors.

Controversial prognostication abilities of natriuretic peptides in clinical trials among T2DM patients

Recent clinical trials have shown that improving metabolic status in HFrEF patients with pre-diabetes and T2DM with glucagon-like peptide-1 [GLP-1] analogue (liraglutide) [57], sodium-glucose co-transporter-2 [SGLT2] (empagliflozine) [58-60], was associated with a tendency to NT-proBNP serum level decrease as a secondary surrogate end point, cardiac protective effect, and beneficial CV outcomes. In contrast, among patients with prediabetes and T2DM without HF serum levels of NT-proBNP remained unaltered regardless of improving glucose homeostasis and decreased CV risk [61]. Interestingly, the change in NT-proBNP serum levels correlated negatively with baseline NT-proBNP levels in T2DM [62]. Additionally, in the DEFINE-HF Trial SGLT2 dapagliflozin did not affect mean NT-proBNP serum levels, but increased the proportion of patients (as diabetics, as well as non-diabetics) experiencing clinically meaningful improvements in HFrEF-related clinical status [63]. It is difficult to speculate a plausible mechanistic reason why GLP-1 analogues and SGLT2 have demonstrated controversial effect on NP circulating levels in patients with T2DM having HF or without it. Interestingly, dipeptidyl peptidase (DPP)-4 inhibitors had been reported to have rather neutral effect than deteriorating impact on myocardium in preclinical studies and early large-scale trials [64-66]. However, on the one hand DPP-4 inhibitors may increase the ability of GLP-1 to stimulate cyclic adenosine monophosphate in cardiac myocytes, and on the other hand they potentiate the effects of stromal cell-derived factor-1 aggravating cardiac fibrosis and indirectly increase in circulating levels of NPs [67]. Finally, an increased risk of HF progression appeared to be a class effect of DPP-4 inhibitors, even in patients without a history of HF [68]. However, other antidiabetic drugs, i.e. metformin, thiazolidinediones, have demonstrated predictably clear impact on circulating levels of NP, i.e. metformin did not increase the concentration of ones, but thiazolidinediones through fluid retention acted as triggers for NP level augment [68].

Conclusions

Natriuretic peptides are useful tool for CV risk stratification among patients with pre-diabetes and T2DM regardless of HF. Presences of HFrEF or HFpEF in T2DM patients may require modification of NP cut-off points to primary diagnose HF and

determine HF-related risks. There are several controversies between clinical outcomes and dynamic of circulating levels of NPs in diabetics treated with GLP-1 agonists and SGLT2 inhibitors that requires to be elucidated in large clinical studies in the future.

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Conflict of interests

Authors have no conflict of interest.

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