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Review

Prognostication of clinical outcomes in diabetes mellitus: Emerging role of cardiac biomarkers

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ABSTRACT

Type 2 diabetes mellitus (T2DM) remains substantial health problem and one of the most prevalent metabolic diseases worldwide. The impact of T2DM on CV mortality and morbidity is embedded through a nature evolution of the disease and is modulated by numerous risk factors, such as hypertension, obesity, dyslipidemia. There is large body of evidence regarding use of the cardiac biomarkers to risk stratification at higher CV risk individuals who belongs to general population and cohort with established CV disease. Although T2DM patients have higher incidence of cardiac and vascular complications than the general population, whether cardiac biomarkers would be effective to risk stratification of the T2DM is not fully understood. The aim of the review is to summarize our knowledge regarding clinical implementation of cardiac biomarkers in risk assessment for T2DM patients. The role of natriuretic peptides, soluble ST2, galectin-3, growth differentiation factor-15, and cardiac troponins are widely discussed.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a substantial public health problem that affects about 10% adult population worldwide [1]. Recent studies have demonstrated that annual global death rate due to T2DM was 1.5 million and an additional 2.2 million deaths were occurred as resulting in cardiovascular (CV) diseases [2,3]. Additionally, nature evolution of T2DM effecting several faces of a life of the patients corresponds to numerous risk factors including hypertension, atherosclerosis, abdominal obesity, diabetes-induced nephropathy, and dyslipidemia [3,4]. Consequently, a CV risk of patients with established T2DM has been gaining from 1.5-fold to 3.5-fold in comparison with none-T2DM individuals [3]. Moreover, prediabetes through impaired mitochondrial metabolism in cardiac and skeletal muscles is able to increase CV risk also [5,6]. For instance, heart failure (HF), atrial fibrillation (AF), chronic kidney disease (CKD), stroke are common causes leading to premature death in populations with prediabetes and established T2DM [7,8]. In fact, the current clinical guidelines refer the presence of these clinical conditions in the list of target organ damage and CV risk charts in diabetic population. Indeed, prediabetes and T2DM were independently associated with developing subclinical direct myocardial damage, microvascular inflammation and endothelial dysfunction, which were recognized as the most important factors contributing to highest risk for clinical CV events [9,10].

According to contemporary strategy for risk stratification in diabetics, single and serial levels of biomarkers (fasting glucose, glycated hemoglobin, glycated albumin, creatinine, and the endogenous secretory receptor for advanced glycation end products [AGEs]) used widely. It has been suggested that these test might improve determining probability of clinical outcomes in pre diabetics and diabetics [11,12]. Indeed, impaired fasting and postprandial glucose levels, as well as concentrations of glycated hemoglobin, creatinine or AGEs well corresponded to CV risk and predicted risk of asymptomatic atherosclerosis, vascular calcifications, and CKD [13,14].

On this way there are several controversies associated with not fully established strong evidence regarding the role of cardiac biomarkers in predicting of mortality in T2DM [15,16]. The first controversy has been relating to optimal choose of cardiac biomarkers to identify CV risk for T2DM patients with asymptomatic CV diseases, while there is limiting evidence that the same biomarkers can be predictors for the diabetes complications (i.e. cardiomyopathy, arrhythmia, HF, or CKD) in diabetics without known CV disease. Next controversy affects an idea that conventional cardiac biomarkers, such natriuretic peptides, soluble ST2, cardiac troponins or galectin-3, growth differential factor-15, may

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Abbreviations

AGEs	advanced glycation end products
AF	atrial fibrillation
CAD	coronary artery disease
CKD	chronic kidney disease
CV	cardiovascular
GDF-15	growth differentiation factor-15
HbA1c	glycated hemoglobin
HF	heart failure
HOMA-IR	homeostasis model assessment of insulin resistance
hs-CRP	high-sensitive C-reactive protein
hs-TnT	high-sensitive troponin T
IL	interleukin
MMP	metalloproteinase
NPs	natriuretic peptides
BNP	brain natriuretic peptide
NT-pro-BNP	N-terminal fragment of pro-brain natriuretic peptide
ST2	suppression of tumorigenicity 2
T2DM	type 2 diabetes mellitus
WAT	white adipose tissue

accurately precede CV risk in diabetics with established CV disease. The aim of the review is to summarize our knowledge regarding predictive role of cardiac biomarkers in T2DM.

2. Natriuretic peptides

Natriuretic peptide (NP) system alterations are involved in pathogenesis of diabetes mellitus and its complications including diabetes-induced cardiomyopathy and angiopathy [17]. NPs are released from cardiac myocytes due to stretching, fluid overload, inflammation, and necrosis [18] Therefore, endothelial cells produce C-type of NP in result of microvascular inflammation, atherosclerosis, endothelial dysfunction and thrombosis [19]. Primary biological effects of NPs, which are promoting diuresis and natriuresis, exerting vasodilation, inhibiting inflammation, differentiation and proliferation of several types of cells, are mediated by appropriate receptors. Therefore, NPs suppressing matrix metalloproteinases (MMPs) in heart, vasculature and kidney inhibit fibrosis [20]. Additionally, NPs are endogenous regulators of cardiovascular, renal, and endocrine homeostasis [21].

The levels of NPs (atrial NP – ANP, brain NP – BNP, and C- NP – CNP) in TDM are variable and they depend on numerous factors. First, NPs having a kidney clearance may be found in elevated concentrations in peripheral blood in diabetic with nephropathy and reduced glomerular filtration rate [22]. Additionally, hyperinsulinemia typically present in abdominal obesity and metabolic syndrome up-regulates receptors for CNPs that lead to decrease circulating levels for them [22,23]. Secondary, patients with abdominal obesity, metabolic syndrome and T2DM without known cardiovascular disease demonstrated lowered levels of N-terminal fragment of proBNP (NT-proBNP) [23,24]. This finding related to epigenetic regulation of both genes' expression of NPs and neprilysin. Indeed, T2DM-induced activation of nuclear factor-κB and transforming growth factor-β1-signalling with increased histone acetyl transferases expressions and augmented H2AK5Ac, H2BK5Ac, H3K18Ac, and H4K8Ac levels associated with neprilysin expression [25]. Altered neprilysin activity mediates increased degradation of NPs and thereby leads to lowered NPs levels in blood. Interestingly, histone acetylation at promoter regions of NPs genes of ANP, BNP and CNP epigenetically regulates increased expressions of ANP, BNP and NEP in myocardium, vasculature and kidney [26]. Third, histone acetylases and histone deacetylases are able to reversibly regulate acetylation in the amino-terminal domains of histone and non-histone proteins, which play a pivotal role in certain cellular processes in T2DM including fibrosis, inflammation, hypertrophy, and oxidative stress that may regulate clearance and metabolism NPs by indirect manner [27,28]. Fourth, volume overload due to fluid retention, stretching of left atrial/ventricle, excessive extracellular fluid volume and low-grading inflammation may also stimulate releasing NPs from cardiac myocytes besides if known CV diseases such as atrial fibrillation, atherosclerosis, myocardial infarction/acute coronary syndrome, hypertension, heart failure and their equivalent (chronic kidney disease with GFR<60 mL/min × 1.73 m^2) are co-existed. Fig. 1 is reported the main triggers that mediate circulating levels of NPs in diabetics.

Although NPs are endogenous regulators of water homeostasis, vasodilation and tissue proliferation acting as physiological competitor of both renin-angiotensin and sympathetic systems, there is evidence that some components of NPs have emerged as important modulators of lipid and glucose metabolism, as well as in insulin sensitivity [29]. In fact, adipocytes of white adipose tissue (WAT) are able to synthesis and release BNP and probably CNP as result in pro-inflammatory cytokine stimulation and thereby modulate lipolytic activity unlike catecholamines and angiotensin-II [30].

Additionally, numerous metabolic actions, which are suitable for NPs, are reported (Fig. 2). There is evidence that NPs predominantly ANP bind to appropriate receptor on adipocyte surface and stimulate membrane-associating cGMP-dependent protein kinase G, which promotes perilipin and hormone-sensitive lipase-mediating triglyceride degradation [31]. There is large body of evidence that ANP may regulate lipolytic effect through the balance of NP receptor expressions for ANP and CNP in adipocytes [32,33]. Yet, insulin may sufficiently reduce ANP-receptor mRNA level, but reciprocally increase CNP receptor mRNA levels via phosphatidylinositol 3-kinase pathway [32]. Consequently, lipolytic activity in WAT can be controlled not just by catecholamines and angiotensin-II via canonic cAMP/PKA pathway, but also by ANP through an independent cGMP-dependent protein kinase G-mediated signalling. Interestingly, the CNP receptors are able to reduce presentation of ANP receptors on adipocytes and decline lipolytic activity of adipose cells locating in subcutaneously, pericardial and perivascular WAT through lowering local NP bioavailability [32–34]. On the other hand, T2DM typically corresponded to dyslipidemia including increased serum triglycerides that are able to escalate BNP secretion through up-regulation of BNP gene(s) on adipocytes [35]. Therefore, oxidized lipids and pro-inflammatory cytokines mediate down-regulation of expression of corin, which is constitutive cardiac serine protease requires having core role for converting pro-ANP to biologically active ANP and exerting cardiac protection [36]. The deficiency of corin in T2DM patients is disputed as an element of cardiac fibrosis and progression of T2DM-induced cardiomyopathy. Although, the NPs' levels independently associate with the main metabolic risk factors in general population as well as in T2DM individuals, the exact molecular mechanisms by which NPs regulate metabolic homeostasis in diabetics remain undefined. Additionally, there is evidence that NPs may protectively impact on myocardium through attenuation of synthesis of apelin and visfatin and suppression of adiponectin releasing [37].

Interestingly, NPs are able to regulate thermogenesis through modification of expression of thermogenic genes (peroxisome proliferator activated receptor gamma coactivator-1 alpha and

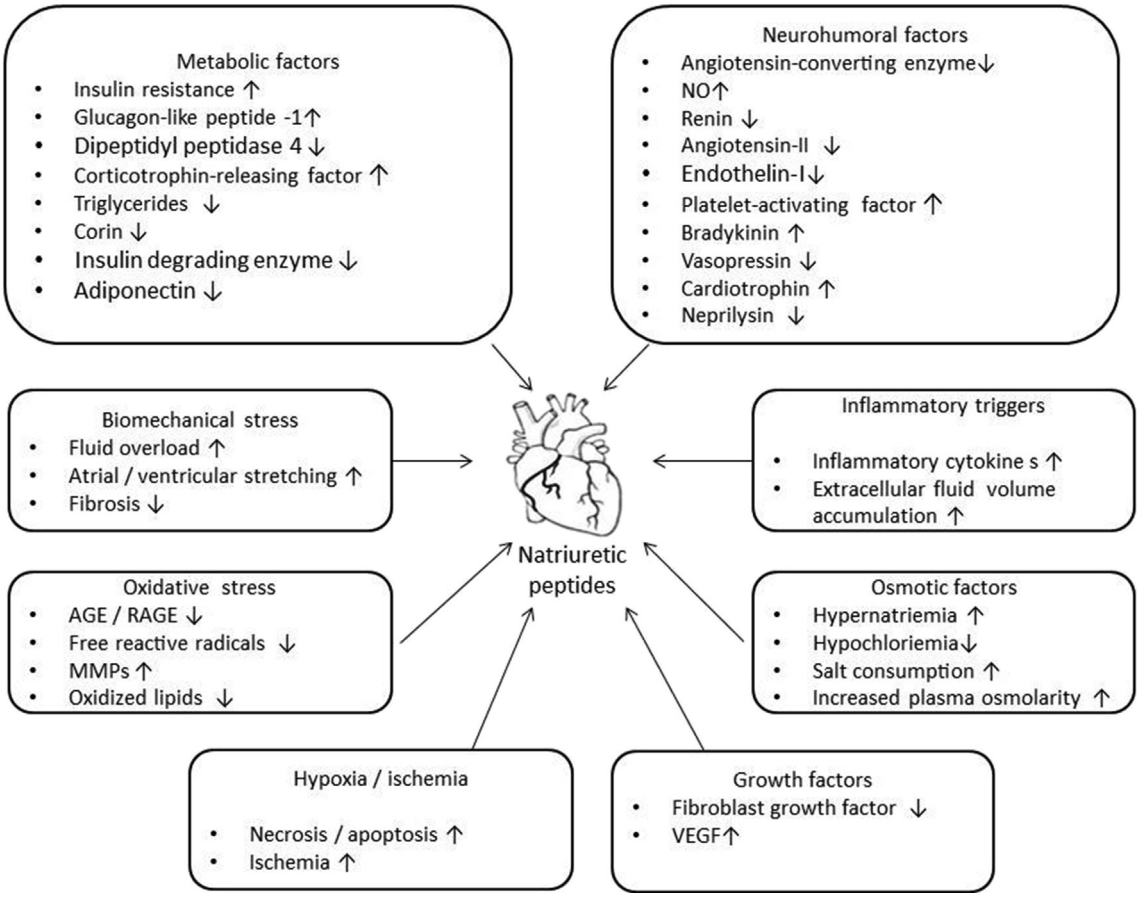

Fig. 1. Triggers that modulate circulating levels of natriuretic peptides in patients with T2DM.

uncoupling protein-1), which located in the white and brown adipose tissue adipocytes. NPs mediate intracellular signal systems, such as p38 MAPK-related and ATF2-dependent pathways, acting as regulators of lipolysis, glucose uptake, free fatty acid metabolism, and mitochondrial energy supply and peroxidation processes, which are embroiled in the thermogenesis and adipose tissue modification [37]. In fact, NPs are cardiomyokines with wide range of biological functions that are not limited auto-paracrine effects and NPs exhibit capabilities for cardiovascular homeostasis and energy metabolism in several tissues.

Current clinical recommendations serve NPs as a powerful non-invasive biomarkers for diagnostic, prediction and stratification of the patients suspecting acute/chronic HF [38,39], while other heart diseases including stable coronary heart disease, myocardial infarction, atrial fibrillation, pulmonary thromboembolism can be predicted with elevated NT-proBNP and NT-proANP levels [40–42].

In T2DM the NPs are reported as surrogate endpoints with possible predictive value. In the SAVOR-TIMI [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction] 53 trial [43] and EXAMINE [Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care] trial [44] major adverse cardiac event (MACE) endpoints and hospital admission for HF were successfully predicted with serial measure of NT-proBNP and NT-proANP levels. Noted, SAVOR-TIMI 53 trial was enrolled T2DM patients with established atherosclerosis, and 11% of them had multiple atherosclerotic artery (coronary, peripheral, or cerebral beds) damages. For 22.2% diabetics CV risk factors were determined without known CV disease. The EXAMINE trial was designed as a project with enrollment of T2DM with established coronary artery disease. In this context, it has been postulated that the absolute risk excess for HF onset/admission and death was attributed with highest NT-proBNP level prospectively evaluated, whereas frequencies of other complications of T2DM (MACE) did not strongly relate to NPs levels [45]. An ability of NPs predict HF in T2DM patients with a known coronary artery disease has evaluated in the ELIXA [Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide)] study [46]. A total of 5450 T2DM patients with previous acute coronary syndrome were enrolled in the study. Serum levels of BNP and NT-proBNP were measured at baseline and at weeks 24, 76, and 108 after study entry. Only 151 patients (3%) met clinical end point defined as HF admission during a median follow-up of 26 months. Analysis of obtained outcomes has shown that peak BNP/NT-proBNP concentrations at the event were significantly ($P < 0.001$) greater in patients who experienced recurrent readmission due to HF. The monthly trend to increase in BNP/NT-proBNP levels strongly predicted other CV outcomes including all cause death, CV death, myocardial infarction, and stroke, while received magnitude of increasing for both NPs appeared to be markedly lower than for HF. Expectedly, the progressive increase of NPs levels for 6 month before HF admission in patients who had experienced in HF was most pronounced to those who did not. However, T2DM patients regardless of a history of HF at the time of HF admission have been demonstrated comparable BNP/NT-proBNP levels. These findings clarified that a trajectory of changes for BNP/NT-proBNP levels may potentially enable earlier identification of T2DM patients at higher risk of HF admission,

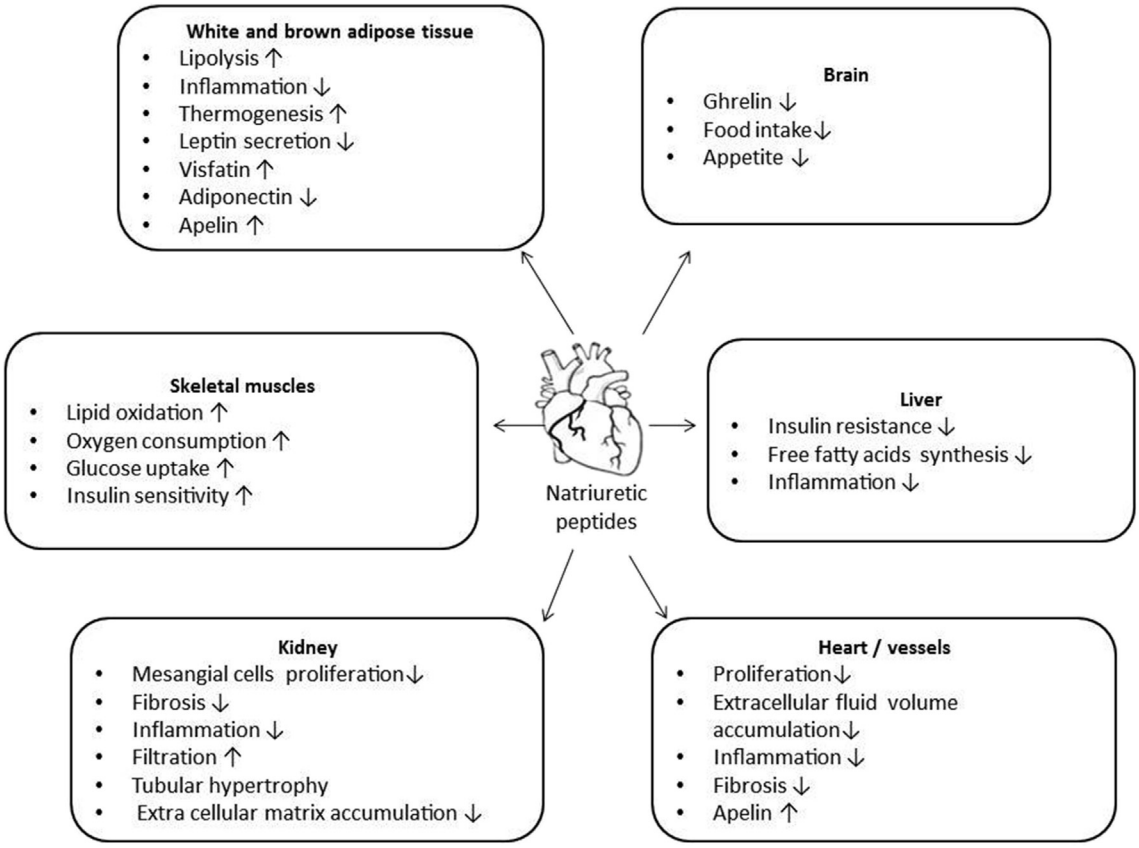

Fig. 2. Metabolic actions of natriuretic peptides.

while specific time intervals needed to NPs monitoring require to be additionally determined.

3. Growth differentiation factor 15

Growth differentiation factor 15 (GDF-15) is stress-responsive cytokine, which belongs to the transforming growth factor beta super family [47]. GDF-15 releases from various cells, such as cardiac myocytes, adipocytes, endothelial cells, mononuclears, due to stress condition and inflammation and plays a pivotal role in regulation of systemic energy metabolism, immunity and fibrosis [48]. Although GDF-15 has been revealed to have anti-apoptotic and anti-inflammatory activities and protective actions for target organs, its role in T2DM patients at higher CV risk is not well defined and has being continued to be widely speculated. Molecular effects of GDF-15 are reported Fig. 3.

The primary molecular target for GDF-15 is membrane-associated p53 protein, which exhibits anti-apoptotic, anti-inflammatory and anti-proliferative effects on target cells. The impact of GDF-15 is mediated by the pro-survival protein activating transcription factor 3 (ATF3), which is negatively regulated by p53 protein. Therefore, GDF-15 acts as an inhibitor of several enzyme systems that are corresponded to cell survival (c-Jun N-terminal kinase, Bcl-2-associated death promoter, and epidermal growth factor receptor, Smad, endothelial nitric oxide synthase, phosphoinositide 3-kinase, and serine/threonine kinase) [48]. The final result of this interaction is suppression of tumor necrosis factor-α and IL-6 production, preventing cardiac hypertrophy, improvement of vascular function, and attenuation of cardiac myocyte and endothelial cell viability.

There is a large body of evidence that expression of GDF-15 in adipose tissue increases with age, body mass index, insulin resistance, prediabetes/T2DM [49,50]. Additionally, levels of GDF-15 positively associate with various CV diseases including HF, stable coronary artery disease, AF and myocardial infarction/acute coronary syndrome [50,51]. In ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial GDF-15 levels predicted major bleeding, all-cause mortality and CV death independently from NPs and high-sensitivity troponin I in patients with atrial fibrillation [52]. In population of PROVE IT-TIMI 22 study patients, who were stabilized after acute coronary syndrome, GDF-15 levels was associated with two-year risk of CV death, myocardial infarction, and HF [53]. Increased levels of GDF-15 exhibited ability to improve predictive value of NT-proBNP for death and HF in post-acute myocardial infarction patients [54].

In XENDOS trial GDF-15 predicted future insulin resistance and impairment of fasting glucose control in pre-diabetic individuals with abdominal obesity [55]. Interestingly, levels of GDF-15 were inversely associated with total cholesterol and high-density lipoprotein cholesterol in general population and in patient with prediabetes and established T2DM, who had participated in the Framingham Offspring Study and the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study [56].

In T2DM patients without known CV disease higher levels GDF-15 were independently associated with all-cause mortality and declining kidney function [57,58], as well as serum GDF15 level was positively correlated with the Framingham risk score and the New Pooled Cohort Equation score [59]. Interestingly, GDF-15 exhibited extremely lowered biological variability and lack of relation to NPs, hs-CRP and smoking status that allow monitoring longitudinal changes [59,60]. Importantly to note the GDF-15 levels in serum were found as unique independent predictor of T2DM-induced

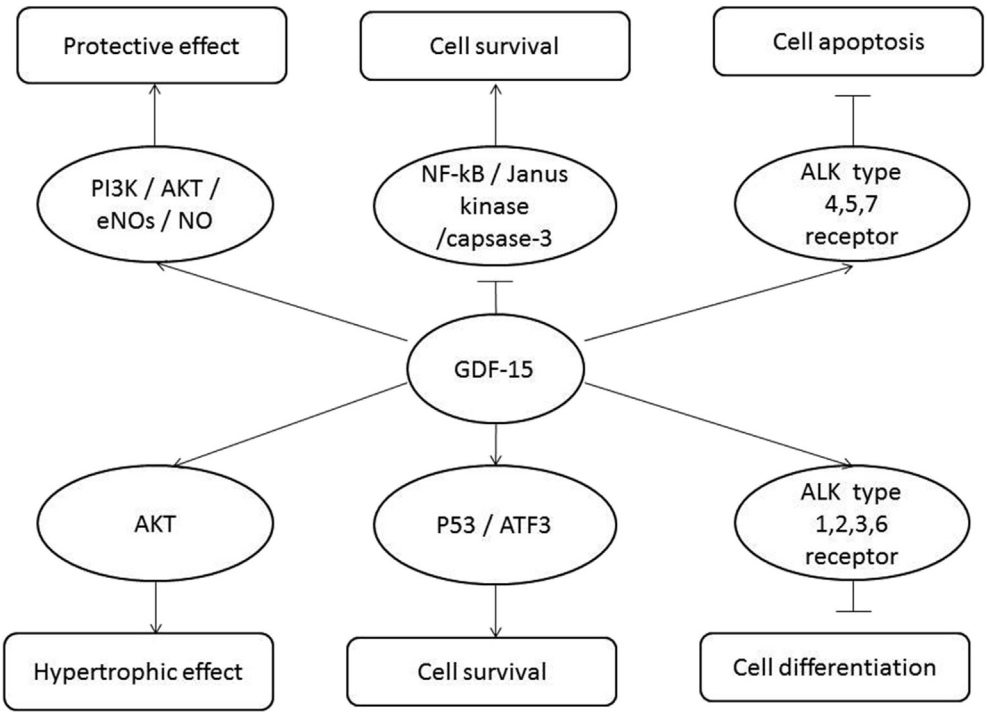

Fig. 3. Biological effects and molecular targets of GDF-15.
Abbreviations: ALK, ALK receptor tyrosine kinase; ATF, activating transcription factor 3; PI3K, phosphoinositol-3-kinase; NF-kB, nuclear factor kappa-B; NO, nitric oxide; eNOs, endothelial NO synthase.

cardiomyopathy [61] and nephropathy [62]. However, GDF-15 and other cardiac biomarkers, such as NT-proBNP and hs-troponin T/I, could represent distinguished discriminative values for pre-diabetics/diabetics. Indeed, Bidadkosh et al. (2017) [63] reported that GDF-15 was rather predictor for renal risk, whereas NT-proBNP and hs-troponin T/I independently predicted CV risk in T2DM patients without known CV disease. In contrast, combined GDF-15 and troponin T/I could be more successful in prediction of clinical outcomes and death in diabetics at higher risk of CV disease [64–66]. All these facts confirm an idea that GDF-15 could suggest as surrogate biomarker in early diagnosis, evaluation and prediction of the outcomes of T2DM regardless presentation of CV disease.

4. Soluble ST2

Soluble suppression of tumorigenicity 2 (sST2) is a member of the of the Toll/IL-1 superfamily, which was found as a biomarker of certain inflammatory condition and fibrosis [67]. sST2 appears to be a decoy receptor of IL 33, which bind with IL-33 and blocks the protective effects of the cytokine, such as reducing myocardial fibrosis and apoptosis, preventing cardiac hypertrophy, and improving myocardial function [68]. sST2 are produced by activated mononuclears, fibroblasts, cardiac myocytes. The main triggers for sST2 are inflammatory cytokines (predominantly tumor necrosis factor-α, interferon-γ and IL-1β), cardiac stretching, ischemia and volume overload, while production of this molecule may be partially extracardiac. For instance, expression of ST2 was observed in alveolar epithelium, and primary human type II pneumocytes was able to release sST2 due to strain [69]. Additionally, mature and progenitor endothelial cells in human heart and vessels are able to express all components of IL-33/ST2 protein axis [70].

The results of the Framingham Heart Study revealed that sST2 is sufficiently elevated in several conditions including atherosclerosis, stable coronary artery disease, acute coronary syndrome/myocardial infarction, atrial fibrillation/flatter, HF, and hypertension [71]. Additionally, serum levels of sST2 modestly but significantly increase in patients with abdominal obesity, prediabetes and diabetes [72]. Interestingly, increased sST2 levels did not correlate with metabolic abnormalities, but significantly 2.31- and 4.00-fold increased a risk of having T2DM in pre-diabetics with third and fourth quartiles (21.3 and 29.1 ng/ml, respectively) of the sST2 levels [72]. At the same time, circulating levels of sST2 in diabetics were higher in older patients to younger, were lower in female to male, as well as it correlated well with triglycerides, liver enzymes (alanine aminotransaminase and γ-glutamyl transferase), fasting glucose, and ectopic fat accumulation [73].

The association of inflammation and fibrosis marker sST2 with all-cause mortality [74], CV mortality, and death due to HF, AF, acute coronary syndrome/myocardial infarction had been investigated previously [75,76]. sST2 is proposed for use as biomarker for risk stratification of patients at higher risk of CV disease including diabetics [77]. The levels of sST2 precede impaired glucose homeostasis and they can predict development of T2DM and its complications, such as accelerating atherosclerosis, T2DM-induced nephropathy and/or retinopathy, critical limb ischemia [78–80].

Advantages and disadvantages of cardiac biomarkers on T2DM patients are reported in Table 1. Whether sST2 levels provide support for the beneficial metabolic and CV effect in T2DM is not fully understood. Although some investigators revealed significant correlations between serum sST2 levels and glycemic control in T2DM individuals [81], but these findings were not confirm an idea that serial measure of sST2 could attenuate a monitoring for CV risk and trend of sST2 levels be useful for adjusting medical treatment [82]. Indeed, in EMPA-REG OUTCOME study and in study entitled "A Safety and Efficacy Study of Canagliflozin in Older Patients [55–80 Years of Age] With Type 2 Diabetes Mellitus" sufficient changes in sST2 levels in T2DM patients without known HF for long-term period of intake of sodium glucose co-transporter 2

Table 1
Advantages and disadvantages of cardiac biomarkers on T2DM patients.

Cardiac biomarker	Advantages	Disadvantages
NPs	• Predict all-cause mortality and CV death • Predict clinical outcomes in pre-diabetics and diabetics • There is trend in concentration changing during treatment of T2DM	• Highest biological variability • Dependence from age, sex, GFR, body mass index • Non-CV disease can influence on serum levels
GDF-15	• Predict clinical outcomes in pre-diabetics • Lack of association with levels of NPs, hs-CRP and smoking status • Predictor of T2DM-induced target organ injury	• Dependence from age and GFR • Moderate biological variability
sST2	• Superior to NPs in prognostication of clinical outcomes • Predict all-cause mortality and CV death • Predict clinical outcomes in pre-diabetics • Lowest biological variability	• Dependence from age and sex • Inferior to NPs in diagnosis of cardiac dysfunction
Galectin-3	• Close association with all-cause mortality and CV death • Lack of correspondence to levels of other biomarkers	• Dependence from age and GFR • Inferior to NPs in diagnosis of cardiac dysfunction and prediction of admission • Lack of changes during treatment of T2DM
hs-Tn T/I	• Independent predictor of CV death and admission to a hospital	• Inferior to NPs in diagnosis of cardiac dysfunction • Lack of changes during treatment of T2DM

Abbreviations: NPs, natriuretic peptides; GDF-15, growth differential factor-15; sST2, soluble suppression of tumorigenicity 2; hs-Tn, high-sensitive cardiac troponins; GFR, glomerular filtration rate.

inhibitors were not found, while clinical outcomes were sufficiently improved [74,82]. In contrast, levels of both NT-proBNP and galectin-3 lowered significantly and strongly corresponded to decreased CV risk and risk of admission due to HF [82]. Thus, a role of sST2 as a target of treatment in T2DM are controversial and requires to be investigated in detail [83], while predictive models shaping on based on sST2 measure exhibited attraction for further studies.

5. Galectin-3

Galectin-3 is a soluble beta-galactoside-binding lectin that is predominantly released by activated macrophages due to inflammatory stimuli and it is known as a marker of cardiac fibrosis and systemic inflammation [84]. Therefore, galectin-3 is able to directly bind to the insulin receptor, and thereby, leads to insulin resistance, lipolysis and glucose intolerance [84,85].

Elevated serum levels of galectin-3 was founds in numerous CV diseases and it associated with adverse clinical outcomes, all-cause mortality, CV mortality and a risk of admission to the hospital [86,87]. Additionally, galectin-3 levels were significantly higher in T2DM patients to pre-diabetics and healthy volunteers [88]. Moreover, galectin-3 levels positively associated with fasting glucose, 2-h plasma glucose, hs-CRP, and homeostasis model assessment of insulin resistance (HOMA-IR) index [88]. Interestingly, increased serum levels of galectin-3 are considered as an adaptive reaction versus inflammatory induced insulin resistance and altered glucose metabolism. Indeed, low levels of serum galectin-3 in T2DM patients were corresponded to insulin resistance [89], overexpression of IL-1β in macrophages, increased accumulation of AGEs and RAGE in pancreatic islets [90]. Moreover, deficiency of galectin-3 production strongly associated with cardiac hypertrophy and fibrosis [91]. On the other hand, galectin-3 activates PPARγ and supports WAT formation acting as modulator of pre-adipocyte proliferation [92,93]. There is evidence that there is a positive association between serum galetin-3 levels and a risk of developing and progression of T2DM-induced nephropathy [94]. Yet, elevated levels of galectin-3 were found as a predictor of diabetic foot ulcers and critical limb ischemia [95]. Taking into consideration these findings there is an assumption that galectin-3 could be a target for therapy at higher CV risk patients, such as T2DM individuals [96]. However, current data obtained in numerous clinical studies, in which several cardiac biomarkers were investigated, appeared to be extremely surprised. Indeed, Alonso et al. (2016) reported that there were no interactions between T2DM and NT-proBNP, hs-TnT, galectin-3, hs-CRP, cystatin-C, and neprilysin relative to a risk prognostication for all-cause mortality and CV death [97]. Multivariable Cox regression analysis did not ever reveal that predictive value of combined biomarkers, such as sST2 or hs-TnT, for survival rate could be improved through embroiling another biomarker including galectin-3. Interestingly, impaired global longitudinal strain appeared to be better biomarker for T2DM cardiomyopathy at early stage that galectin-3 [98]. Moreover, reduced cardiac contractile reserve and altered insulin sensitivity in HF patients with T2DM did not to have an independent impact on serum galectin-3 levels [99,100]. Probably galectin-3, which used to implement in the general population to predict developing of HF [101], did not turn out powerful prognosticator for T2DM patients.

6. Cardiac troponins

High-sensitivity cardiac troponins are well-known biomarkers of myocardial injury [102]. Current clinical guidelines are recommended to use serial measure of hs-Tn T/I as diagnostic and prognostic tools in patients with acute coronary syndromes, myocardial infarction, as well as to enhance risk stratification for HF patients [103,104]. In fact, a risk of death in troponin positive individuals with acute coronary syndrome was significantly higher in comparison to troponin negative patients [104]. There is large body of evidence regarding that hs-Tn T/I levels were independent predictors of incident hospitalisation due to atrial fibrillation/flatter, HF, stroke, stable coronary artery disease, pneumonia, but hs-Tn T/I levels did not improve a risk stratification in a community-based cohorts [105–107].

Additionally, serum levels of cardiac troponins are frequently elevated in patients with HF, metabolic syndrome, T2DM, chronic kidney disease and positively correlate with the risk for all-cause and CV mortality [108–110]. Although serum levels of hs-TnT corresponded positively to T2DM-induced myocardial injury, some antidiabetic drugs (insulin, thiazolidinediones, metformin) did not impact on hs-TnT levels, whereas tight glucose control was achieved and preventing atherosclerosis was verified [111–113]. Thus, cardiac troponins can predict a CV risk, but they are not suitable for guided therapy in T2DM. Whether hs-TnT levels are the best tool to improve predictive value for other cardiac biomarkers, such as NT-proBNP and sST2, is not fully understood and required to be evaluated in the future.

7. Conclusion

In conclusion cardiac biomarkers, such as NPs, GDF-15, sST2, galectin-3 and cardiac troponins, have been reported predictive potency to risk stratification in general population with and T2DM patients. Although all these markers were useful for prognostication of all-cause and CV mortality in T2DM patients with known CV diseases, only sST2 in combination nether NPs or cardiac troponins exhibited an ability to improve discriminative value for clinical outcomes in pre-diabetics and diabetics regardless of established CV diseases. Future investigations should be addressed to solve controversial whether these biomarkers are targets for guided therapy of T2DM. Large clinical trials are required to clearly understand the role of serial measure of cardiac biomarkers in risk stratification in T2DM.

Conflicts of interest

None declare.

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