

The Role of Cardiac Biomarkers in Predicting of Mortality in Diabetic Patients

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic diseases that associated with increased risk for cardiovascular (CV) diseases and newly CV events. Although CV risk assessment is incorporated in primary and secondary prevention strategies to improve morbidity and mortality that are applied in diabetic patient, it is important to stratify individuals at high CV risk not just prior diabetic complication, but at early stages of development of the CV diseases. The aim of the editorial comment is to discuss possible predictive role of cardiac biomarkers in T2DM. Cardiac biomarkers may contribute to improved prediction of CV mortality and CAD incidences in T2DM. It has suggested that measurement of serum levels of hs-CRP, galectin-3, NPs, and hs-cTnT probably allows the identification of T2DM patients the most at risk of CV events. Future directions are associated with discovering of novel biomarkers and optimal combinations of recently used markers to provide additional prognostic information beyond what is available with other traditional CV risk factors.

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Key words: Diabetes mellitus; Cardiovascular disease; Risk; Biomarkers; Prediction; Mortality

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Abbreviations

CAD: coronary artery disease;

CRP: C-reactive protein;

GDF-15: growth differentiation factor-15;

IL: interleukin;

hs-cTnT: highly-sensitivity cardiac troponin T;

NPs: natriuretic peptides;

ST2: a member of the interleukin-1 receptor family protein of tumorigenety;

T2DM: type two diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has known as one of the most prevalent metabolic diseases that undoubtedly associated with increased risk for cardiovascular (CV) diseases and newly CV events^[1]. This risk might be contributed through nature evolution of the disease and effect of coexisting CV risk factors, such as hypertension, obesity, dyslipidaemia, that are becoming more prevalent in diabetic patients and may increase CV risk directly. Indeed, there is large body of evidence regarding coronary artery calcified plaque, carotid artery intima-media thickness, elevated blood pressure, worse kidney function, prolonged QT interval, poor glycemic control, and albuminuria might predict all cause and CV mortality in the general population of patients with T2DM^[2]. Therefore, patients with T2DM have higher incidence of macrovascular disease and thrombotic complications than the general

population. Moreover, the last decades of investigations have been focused on diabetic-induced altered gene expression, cellular signaling, and cellular metabolism affected various tissue and organs contributed different sides in pathogenesis of diabetes^[3]. In fact, needing in markers reflected nature evolution of diabetes, CV risk, a response of care, which could probably demonstrate predictive value are required.

Although CV risk assessment is incorporated in primary and secondary prevention strategies to improve morbidity and mortality that are applied in diabetic patients, it is important to stratify at high risk individuals not just prior diabetic complications, but at early (including asymptomatic) stages of development of the CV diseases^[4,5]. Additionally, serial measurements of several circulating biomarkers might be considered to receive valuable information for both risk assessment and predictors of clinical outcomes in T2DM patient population. Several well known T2DM-related biomarkers, i.e. glycated hemoglobin, glycated albumin, and the endogenous secretory receptor for advanced glycation endproducts, may modulate risk related to atherosclerosis^[6]. Therefore, previous studies explored the association of T2DM development with arterial stiffness, aortic pulse wave velocity, thickness biomarkers, but the conclusions are either inconsistent or incomprehensive. In this context, cardiac biomarkers remain to be attractive for predictive models in T2DM patients. However, the role of cardiac biomarkers in predicting of mortality in diabetic patient population has not been fully established and appears to be controversially. The first controversy relates to the possibility to being elevated cardiac biomarker levels in diabetic patients beyond documented CV diseases^[7]. Alternatively, there are reports that increased circulating level of several cardiac biomarkers in diabetic patients with heart failure or chronic kidney disease might be higher than in none-diabetic population^[8]. All these findings require serious explanations regarding probability, sensitivity, specificity, and any perspective to use of cardiac biomarkers aimed CV and mortality assessment in diabetic population. The aim of the editorial comment is to discuss possible predictive role of cardiac biomarkers in T2DM.

BIOMARKERS AND CV COMPLICATIONS IN DIABETICS

As well known a prominent attribute of diabetic induced CV complications is accelerated atherosclerosis, endothelial dysfunction, low-intense inflammation, and worsening of tissue repair as result in insulin resistance, hyperglycaemia and oxidative stress^[9-12]. All these factors contribute a development of coronary artery disease, diabetic cardiomyopathy, heart failure, arrhythmia, thromboembolism, and risk of suddenly death^[5,13-16]. Appropriately, biomarkers might reflect appropriate faces of multifactorial pathogenesis of disease and pre-

dict CV mortality. The classification of cardiac biomarkers involved in the T2DM development is given in table 1.

BIOMARKERS OF INFLAMMATION IN DIABETIC POPULATION

Low-intense inflammation plays a pivotal role in the etiology of T2DM. Recent investigations have shown that over production of pro-inflammatory cytokines is the essential step in glucotoxicity and lipotoxicity induced mitochondrial injury, oxidative stress, insulin resistance, and beta cell apoptosis in T2DM. However, extended spectrum of biological markers including C-reactive protein, galectin-3, tissue necrosis factor-alpha, interleukin (IL)-6, IL-1, IL-10, IL-18, resistin, adiponectin, leptin, vistafin, tissue plasminogen activator, fibrinogen, adhesion molecules and heptoglobins, has demonstrated a sufficient relationship with T2DM-related complications and outcomes. Some of them, i.e. C-reactive protein (CRP), galectin-3, can be important both in diagnosis and in the evaluation of CV diseases in diabetic population^[17-19]. Therefore, several novel inflammatory biomarkers, such as growth differentiation factor-15 (GDF-15), lectin-like oxidized low density lipoprotein receptor-1, myeloid-related protein 8/14, pentraxin 3, pregnancy-associated plasma protein-A, are currently recognize markers of vascular remodelling, atherosclerosis, plaque instability, CV outcomes in none-diabetic patients with documented CAD^[20-24].

Although an adequate risk assessment remains to be the most challenging in diabetic individuals classified into intermediate CV risk category, not all mentioned above biomarkers could help to stratify the patients correctly. Moreover, current clinical recommendations of numerous esteemed scientific societies predominantly provide to use a routine measurement of high sensitive CRP^[25]. Unfortunately, recent studies confirmed lack of CRP specificity and causal relationship between CRP concentration and CV risk in general population subjects^[26]. Therefore, there was not a sufficient dependence CRP on other classical CV risk factors^[27]. Moreover, it is still not clear whether use of biomarker platform would be useful for increase specificity and sensitivity of CRP. All these discrepancies require discover novel biomarkers with high diagnostic and predictive value that could use in diabetics unless CV diseases for risk stratification.

Galectin-3 is an endogenous, soluble beta-galactoside-binding lectin, which is highly expressed in a variety of cells and occurs in the cell nucleus, the cytoplasm and on the surface of certain cells and regulates cell-to-cell cooperation, immunity, and extracellular interactions^[27]. The main biological role of galectin-3, as reported, is modulation of biological recognition processes, regulation of

Table 1 The classification of cardiac biomarkers involved in the T2DM development.

Biomarker groups	Names of biomarker members
Biomarkers of endothelial dysfunction	ADMA, endothelial-derived microparticles, small-size endothelial-derived microparticles, endothelial progenitor cells, micro RNAs (miRNA-125a-5p, miRNA-342-3p, miRNA-365b-3p), matricellular proteins (osteopontin, osteoprotegrin, osteonectin, thrombospondin)
Biomarkers of low-intense inflammation	C-reactive protein, galectin-3, tissue necrosis factor-alpha, IL-6, IL-1, IL-10, IL-18, resistin, adiponectin, leptin, vistafin, tissue plasminogen activator, fibrinogen, adhesion molecules, heptoglobins, soluble ST2, lectin-like oxidized low density lipoprotein receptor-1, myeloid-related protein 8/14, pentraxin 3, pregnancy-associated plasma protein-A
Biomarkers of oxidative stress	Placental growth factor, lectin-like oxidized low density lipoprotein receptor-1, soluble fms-like tyrosine kinase 1, 8-epi-prostaglandin F2alpha
Biomarkers of cardiac biomechanical stress	Natriuretic peptides, copeptine, cardiac specific troponins, cardiotrophin-1
Biomarkers of vascular remodelling	GDF-15, lectin-like oxidized low density lipoprotein receptor-1, myeloid-related protein 8/14, pentraxin 3, pregnancy-associated plasma protein-A, matrix metalloproteinases and their tissue inhibitors, matricellular proteins (osteopontin, osteoprotegrin, osteonectin, thrombospondin)

ADMA: asymmetric dimethylarginine; IL: interleukin; GDF-15: growth differentiation factor-15; miRNA: micro RNA.

fibroblast proliferation and matrix synthesis that lead to fibrosis and extracellular remodelling^[28]. Therefore, galectin-3 plays an important role in inflammation, coagulation, thrombosis, malignancy, and metastatic process. Overall, galectin-3 is considered a marker of vasculopathy and vascular remodelling that accompanies endothelial response, inflammation, proliferation, and immunity in general population as well as in subjects with established CV diseases and diabetes^[29].

Galectin-3 was proposed as a powerful predictor of heart failure and CV mortality, and then it became a useful prognostic marker in diabetic subjects with documented CV disease including heart failure^[30,31]. The main advantage of galectin-3 is being closely relationship between plasma concentration of this marker and CV risk^[32]. Ozturk *et al*^[33] reported that galectin-3 was found to be a significant independent predictor of coronary atherosclerosis in T2DM patients. However, galectin-3 was not found to be superior to CRP, natriuretic peptides, soluble ST2, or GDF-15 as a predictor of mortality^[34]. Although soluble ST2 and GDF-15 were recognized a significant predictor of CV outcomes in heart failure patients, their predictive value was not particularly stronger than galectin-3 and N-terminal pro-B-type NP in T2DM. Whether galectin-3 would be novel predictive biomarker for T2DM patients is not fully understood, although more evidences reflect opinion of experts that it is possible. Large sample size investigations are required to explain conflicting results that have generated recent clinical trials^[35].

NATRIURETIC PEPTIDES

Natriuretic peptides (NPs) are recognized as markers of biomechanical cardiac stress that are secreted resulting in stretching cardiac wall / volume overload and they have demonstrated high diagnostic and predictive value for heart failure^[36-38]. In fact, NPs have a wide range of protective functions, including vasodilation, natriuresis, diuresis, lipolysis, weight loss, lusitropy, and improved tissue insulin sensitivity. Although NPs are biomarkers for CV risk and mortality in a large community-based cohort free of heart failure, the clinical significance of elevated NP level has been found to differ in diabetics and non-diabetics, as well as in obese and non-obese individuals^[39,40]. Recent evidences suggest important metabolic effects of the NPs, which have been shown to activate lipolysis, enhance lipid peroxidation and mitochondrial respiration^[40]. Taken into consideration these findings, NPs are considered target for therapeutic strategies in cardiometabolic diseases, while NPs had the inverse association with T2DM incidences^[42]. Indeed, recent clinical trials have revealed that although very high circulating NP level characterizes severity of left ventricular dysfunction and heart failure, a consistently reduced NP plasma level is observed in T2DM and obesity^[42]. However, a low circulating NP level may also predict the risk of new onset T2DM. Alternatively, the results of The Multi-Ethnic Study of Atherosclerosis (MESA) have shown that circulating N-terminal pro-B-type NP (NT-proBNP) had a biphasic association with T2DM in which the risk of diabetes incident decreased within so called “physiological range” of changes in NT-proBNP level^[43]. Inversely, increased risk of T2DM incidences has raised proportionally NT-proBNP concentrations increase probably in response to pathophysiological conditions leading to high levels of NT-proBNP. The EXAMINE trial showed that brain NP concentration at baseline in patients with T2DM and recent acute coronary syndromes randomly assigned DPP-4 inhibitor alogliptin or placebo plus standard treatment for diabetes decreased significantly and similarly in the two groups. Interestingly, the favourable results

of alogliptin on composite events of cardiovascular death and hospital admission for heart failure did not differ by baseline brain NP concentration^[44]. In this context it is unclear whether would NP-guided therapy of heart failure in T2DM patients be useful or not. It seems to be that measuring NPs has high diagnostic and predictive value for diabetics, but NP-guided therapy might have serious limitations required more investigations in future.

ENDOTHELIAL-DERIVED MICROPARTICLES

T2DM may negatively affect tissue reparation via involving various intracellular metabolic pathways, stress responses, lipotoxicity, cytoskeletal rearrangement, angiogenesis, as well as apoptotic signalling, cell-to-cell cooperation, and other functions of targeting cells. Microparticles (MPs) are defined a heterogeneous population of vesicles (diameter 100-1000 nm) that are released by cellular vesiculation and fission of the membrane of parent cells. Currently MPs are discussed powerful paracrine regulators of target cell functions affected growth of tissue, reparation, vasculogenesis, inflammation, and apoptosis^[45]. MPs originated from different cells (endothelial cells, mononuclears, platelets) play a pivotal role in intercellular information exchange through transfer of active molecules, microRNA, peptides, hormones, inflammatory factors, growth factors, etc.^[46]. Although elevated level of MPS originated from endothelial cells, mononuclears, platelets, were found in T2DM, obesity, heart failure, stable CAD, asymptomatic atherosclerosis, acute coronary syndrome, the signature of MP was different for each case. It has suggested that imbalance between numerous of MPs derived from activated and apoptotic endothelial cells might relate to endothelial dysfunction and predict outcomes independently T2DM presentation^[47]. Although elevated level of apoptotic endothelial cell-derived MPs have demonstrated their prediction for heart failure development and clinical outcomes^[48-50], the role of activated endothelial cell derived MPs is still not clear. Overall, the perspectives regarding individualization of risk stratification among T2DM using immune phenotypes of MPs appears to be attractive, although more evidences are required to understand the role of MPs in T2DM and CV diseases.

MATRICELLULAR PROTEINS

Matricellular proteins belong to family of multifunctional growth factors that are main components of the extracellular matrix which regulate bone developing, vascular remodelling, and tissue regeneration^[51]. Although matricellular proteins (osteopontin, osteoprotegrin, osteonectin, thrombospondin) are surrogate biomarkers of vascular calcification and endothelia dysfunction in diabetes, obesity, atherosclerosis, dyslipidemia, the predictive role of these biomarkers in persons with CV disease and T2DM are still not understood because evidences are limited^[52,53]. It has suggested that over production of matricellular proteins in diabetes and CV diseases may consider as response to prevent vascular calcification, reduce obesity-associated inflammation, and improve insulin sensitivity^[54,55]. However, the interrelation between CV mortality and circulating level of matricellular proteins in T2DM is needed to be established.

CARDIAC TROPONINS

Cardiac troponins are urgent biomarkers of myocardial injury and they are currently recommended to use for both diagnostic and prognostic purposes in acute coronary syndrome^[56]. The patterns

of temporal change in highly-sensitivity troponin-T (hs-cTnT) may reflect a subclinical myocardial injury that is suitable for diabetes cardiomyopathy, heart failure and stable CAD. Therefore, mild elevated level of highly-sensitivity circulating cardiac troponins was found in untreated T2DM patients independently of traditional CV risk factors unless myocardial infarction^[57]. Recent clinical trials have shown that serum level of hs-cTnT has well associated with CV mortality and CAD incidences in individuals with T2DM, metabolic syndrome and possible obese^[58-60]. Future studies are required to determine whether cardiac troponins might use in biomarker-guided therapy to prevent progression of subclinical myocardial injury.

COPEPTIN

Copeptin known as the C-terminal fragment of arginine vasopressin prohormone is considered to be a stable, reliable, and clinically useful surrogate marker of biomechanical stress. Elevated level of copeptine was recently found in T2DM patients^[61], CV disease and kidney disease subjects^[62-64]. Moreover, elevated copeptin predicted an increased risk for T2DM independently of established conventional risk factors, including fasting glucose, C-reactive protein and insulin level^[64]. Previous clinical studies have been shown that copeptine appeared to be able to predict heart disease, heart failure and CV death differentially in diabetic individuals^[65]. According opinion of investigations, all these findings might have sufficient implications for risk assessment, novel antidiabetic treatments, and metabolic side effects from arginine vasopressin system modulation.

Overall, a wide spectrum of cardiac biomarkers as expected might have a prognostic value, although clinical evidences were received not for all of them (Table 2). Multiple, complementary biomarkers of biomechanical stress and endothelial dysfunction appears to be attractive in this context. The principal scheme to identification of vulnerable patient with T2DM is given on Figure 1. As one can see, approach based on multiple biomarker use reflected various faces of TDM development is appeared superior compared with single biomarker implementation at different stage of T2DM and CV disease.

In conclusion, an assessment of diabetic patients is challenging in clinical practice resulting in frequently atypical presentation of signs and symptoms, as wells as under recognizing CV risk. Cardiac biomarkers may contribute to improved prediction of CV mortality and CAD incidences in T2DM, but novel clinical data are required to understand what is critical numerous and combinations of markers are enough to increase risk stratification. Measurement of serum levels of hs-CRP, galectin-3, NPs, and hs-cTnT probably allows the identification of T2DM patients the most at risk of CV events, although the predictive role of other cardiac biomarkers, i.e.

soluble ST2, GDF-15 is not still understood^[66,67]. Future directions are associated with discovering of novel biomarkers and optimal combinations of recently used markers to provide additional prognostic information beyond what is available with other traditional CV risk factors.

CONCLUSIONS

In brief, PCSK9 inhibitors can cause 50-60% reduction in LDL cholesterol levels, resulting in to significant decline in cardiovascular events without any significant adverse effects. Larger long term, double blind trials are necessary to confirm the safety and efficacy of these agents in the prevention of cardiovascular diseases. The FOURIER study (NCT01764633) which is a randomized, placebo controlled ongoing trial aims to provide a more accurate assessment of the cardiovascular benefit of evolocumab. The FOURIER study is involving 27,500 high-risk patients with CVD who are receiving background statin therapy. The primary end point is a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization. Other trials of alirocumab and bococizumab to evaluate cardiovascular outcomes are also in progress (NCT01663402, NCT01975376, and NCT01975389).

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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Table 2 Evidences of predictive value regarding cardiac biomarkers in T2DM patients.

Biomarker	Findings of clinical trials	Ref.
Galectin-3	Elevated level of galectin-3 independently predicts coronary atherosclerosis in T2DM patients	[33]
Copeptin	Elevated copeptin predicts an increased risk for T2DM, heart disease, heart failure and CV death	[64, 65]
Natriuretic peptides	Circulating NT-proBNP and BNP levels are reduced in obesity and predict the risk of T2DM.	[43]
Endothelial-derived microparticles	Numerous of MPs derived from activated and apoptotic endothelial cells might relate to endothelial dysfunction and predicts outcomes in T2DM patients. Predictive value requires confirmation	[47]
Matricellular proteins	Matricellular proteins in T2DM are considered a marker of vascular calcification and atherosclerosis. Predictive value is not still defined	[54, 55]
Cardiac troponins	Cardiac troponins predict diabetes cardiomyopathy, heart failure and CV risk in T2DM	[57-60]
soluble ST2	soluble ST2 does not predict CV disease, fatal and non-fatal heart failure, T2DM, and death in a healthy general population. Predictive value is not still defined	[66]
GDF-15	Elevated GDF-15 levels are associated with CV diseases, heart failure, atherosclerosis, endothelial dysfunction, obesity, insulin resistance, T2DM, and chronic kidney diseases in diabetes. Predictive value in T2DM is not still defined	[67]

NT-proBNP: N-terminal pro-B-type natriuretic peptide; MPs: microparticles; GDF-15: growth differentiation factor-15; ST2: a member of the interleukin-1 receptor family protein of tumorogenity.

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