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Cardiovascular Biomarkers in Routine Screening of Diabetic Patients

Alexander E Berezin*

Cardiology Unit, Internal Medicine Department, State Medical University, Mayakovski av., Zaporozhye, Ukraine

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. CV biomarkers may contribute to improved prediction of mortality and CV events in T2DM. It has suggested that measurement of serum levels of hs-CRP, galectin-3, natriuretic peptides, fibroblast growth factor-23, α-klotho, and hs-cTnT probably allows the screening of diabetes patients 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.

Keywords: Diabetes mellitus; cardiovascular disease; Risk; Biomarkers

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 tumorogenity; T2DM: Type 2 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 and individuals with known CV disease [3,4]. Indeed, epidemiologic analyses have exhibited a strong association between T2DM and micro- and macrovascular disease [4]. Vascular dysfunction caused by metabolic abnormalities in patients with T2DM is associated with accelerated atherosclerosis and increased risk of myocardial infarction (MI), stroke, and peripheral arterial disease. Patients with T2DM are at two to four fold higher CV risk as compared to non-diabetic individuals [2-4]. The Canadian Primary Care Sentinel Surveillance Network (CPCSSN), which is a multi-disease surveillance system based on primary care electronic medical record data, has revealed that large proportion (65%) of T2DM patients without established atherosclerotic CV disease presented with 2 or more CV risk factors including: hypertension (62%), dyslipidemia (33%), active smoking (13%), and obesity (43%) [5]. Additionally, a large proportion of T2DM patients (19.5%) had a diagnosis of cardiac-specific issues including coronary artery disease (CAD)/MI/heart failure (not due to MI/CAD), or arrhythmia, and, however, almost 82% of T2DM patients had either established atherosclerosis [5].

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 [6]. 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 [7,8]. Additionally, serial measurements of circulating biomarkers might be considered to receive valuable information for risk assessment and 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 end-products, may modulate risk related to atherosclerosis [9]. Therefore, previous studies explored the association of T2DM development with arterial stiffness, aortic pulse wave velocity, arterial wall thickness, but the conclusions are either inconsistent or incomprehensive [10-12]. Indeed, using up-to-date meta-analysis Yapei et al. [10] reported being a strong association between T2DM and arterial stiffness, the augmentation index, aortic pulse wave velocity, brachial-ankle pulse wave velocity, carotid intima-media wall thickness in separately diabetic populations, i.e., in both white and Asian populations. In clinical study provided by Wang et al. [11] arterial wall thickness, calcification, and increased arterial stiffness were found common biomarkers of early arterial dysfunction in T2DM individuals. Contrary, Avci et al. [12] reported that increased arterial stiffness and arterial wall thickness are probably markers of systemic atherosclerosis in T2DM population and these biomarkers might not consider a predictor of early diabetic arterial dysfunction.

In this context, cardiac biomarkers remain to be attractive for

***Corresponding authors:** Alexander E. Berezin, Professor, MD, PhD, Consultant of Cardiology Unit, Internal Medicine Department, State Medical University, 26, Mayakovski av., Zaporozhye, Ukraine, Postcode 69035, Tel: +380612894585; E-mail: dr_berezin@mail.ru

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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 [13]. 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 [14]. 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 [15-18]. All these factors contribute a development of coronary artery disease, diabetic cardiomyopathy, heart failure, arrhythmia, thromboembolism, and risk of suddenly death [8,19-22]. Appropriately, biomarkers might reflect appropriate faces of multifactorial pathogenesis of disease and predict 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 [23-25]. Therefore, several novel inflammatory biomarkers, such as growth differentiation factor-15 (GDF-15), fibroblast growth factor-23, 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 [26-30].

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 [31]. Unfortunately, recent studies confirmed lack of CRP specificity and causal relationship between CRP concentration and CV risk in general population subjects [32]. Therefore, there was not a sufficient dependence CRP on other classical CV risk factors [33]. 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 [33]. The main biological role of galectin-3, as reported, is modulation of biological recognition processes, regulation of fibroblast proliferation and matrix synthesis that lead to fibrosis and extracellular remodelling [34]. Therefore, galectine-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 [35].

Galectin-3 was proposed as a powerful predictor of heart failure and CV mortality, and then it become a useful prognostic marker in diabetic subjects with documented CV disease including heart failure [36,37]. The main advantage of galectin-3 is being closely relationship between plasma concentration of this marker and CV risk [38]. Ozturk et al. [39] 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 [40]. 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 [41].

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, FGF-23, 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 Dimethyl Arginine; IL: Interleukin; GDF-15: Growth Differentiation Factor-15; FGF: Fibroblast Growth Factor; miRNA: Micro RNA

Table 1: CV biomarkers in the diabetic risk screening.

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 [42-44]. 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 none-diabetics, as well as in obese and non-obese individuals [45,46]. Recent evidences suggest important metabolic effects of the NPs, which have been shown to activate lipolysis, enhance lipid peroxidation and mitochondrial respiration [47]. Taken into consideration these findings, NPs are considered target for therapeutic strategies in cardio metabolic diseases, while NPs had the inverse association with T2DM incidences [48]. 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 [49]. 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 [49]. 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 [50]. 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, lipotoxity, 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 paretal cells. Currently MPs are discussed powerful paracrine regulators of target cell functions affected growth of tissue, reparation, vasculogenesis, inflammation, and apoptosis [51]. 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. [52]. 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 [53]. Although elevated level of apoptotic endothelial cell-derived MPs have demonstrated their prediction for heart failure development and clinical outcomes [54-56], 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 [56]. 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 [58,59]. 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 [60,61]. 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 [62]. 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 [63]. 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 [64-66]. 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 [67], CV disease and kidney disease subjects [68-70]. Moreover, elevated copeptin predicted an increased risk for T2DM independently of established conventional risk factors, including fasting glucose, C-reactive protein and insulin level [70]. 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 [71]. According opinion of investigations, all these findings might have sufficint implications for risk assessment, novel antidiabetic treatments, and metabolic side effects from arginine vasopressin system modulation.

Growth Differentiation Factor-15

GDF-15 (recently known as macrophage inhibitory cytokine-1) is a member of the transforming growth factor beta (TGF-β) super family [72]. It is widely presented in the various cells (macrophages, vascular smooth muscle cells, adipocytes, cardiomyocytes, endothelial

cells, fibroblasts), tissues (adipose tissue, vessels, tissues of central and peripheral nervous system) and organs (heart, brain, liver, placenta), where it has been shown to play an important role in the regulation of the inflammatory response, growth and cell differentiation [73].

The main sources of GDF-15 releasing in diabetes are macrophages, white adipose tissue and liver cells. However, the over expression of GDF-15 on surfaces of cardiomyocites in diabetics unless CV diseases including heart failure was not found. Probably, patients with established ischemic-induced CV disease might have extended source for GDF-15 releasing.

The triggers of production of GDF-15 are biomechanical stress, ischemia, anoxia and inflammatory cytokines (tumor necrosis factor alpha, interleukins (IL)-2, IL-4, IL-6), angiotensin II, macrophage colony stimulating factor, and TGF-β. The direct molecular biological target of GDF-15 is p53 protein, which is induced by oxidative stress and has anti-apoptotic effects on target cells. This effect closely associates with the pro-survival protein activating transcription factor 3 (ATF3), which is negatively regulated by p53 protein expression. Therefore, GDF15 inhibits c-Jun N-terminal kinase, Bcl-2-associated death promoter, and epidermal growth factor receptor, as well as activates various intracellular signaling pathways, i.e., Smad, endothelial nitric oxide (eNO) synthase, phosphoinositide 3-kinase, and serine/threonine kinase. The final result of this interrelation is suppression of both tumor necrosis factor alpha and IL-6 synthesis, protect of pressure-induced cardiac hypertrophy, improvement of vascular integrity, and increasing cardiomyocyte and endothelial cell viability [74].

Recent clinical studies have shown that elevated level of GDF-15 was found as a marker of asymptomatic atherosclerosis, coronary artery disease, heart failure, hypertrophic cardiomyopathy, pulmonary hypertension, respiratory and kidney failure, ineffective erythropoiesis in several anemias [75]. Among T2DM population serum level of GDF-15 was positively associated with body mass index, body fat, fasting glucose level, glycated hemoglobin, insulin resistance index, waist to height ratio, age, arterial blood pressure, triglycerides, creatinine, glucose, hs-CRP, diabetic nephropathy and inversely with insulin, anemia [76-78].

In fact, GDF-15 was found a predictive biomarker in CV mortality in general population and among subjects with asymptomatic atherosclerosis [79]. Accumulating evidences have shown that GDF15 could associate with the development and prognosis of T2DM. Although GDF-15 has been reported to be involved in energy homoeostasis and weight loss, to have anti-inflammatory properties, and to predict CV diseases and CV events in general or established CV disease population, there is no large of body of evidence regarding predictive role of elevated GDF-15 in T2DM subjects.

Fibroblast Growth Factor-23

Fibroblast growth factor-23 (FGF-23) is a circulating 32-kDa peptide secreted by the osteocytes in response to hyperphosphatemia and calcitriol therapy. FGF-23 acts though α-Klotho, which is a trans-membrane protein that appears to be involved in CV aging. It has found that FGF-23 exclusively activates appropriate FGF receptors on target myocytes to stimulate phospholipase Cγ/calcineurin/nuclear factor of activated T cell signalling and proliferative response [80].

FGF-23 is constantly elevated in patients with advanced chronic kidney disease, due to several reasons including phosphate overload and diabetes. Recently FGF-23 was identified as a surrogate biomarker of pre-clinical atherosclerosis, assessed as arterial stiffness in diabetic patients and no previous CV events [81]. Therefore, elevated level of FGF-23 was associated with an increased risk of CV mortality or heart failure development [82]. However, the predictive role of elevated FGF-23/α-Klotho in diabetic patients is still not fully understood.

Conclusions

There is a wide spectrum of CV biomarkers as expected might have a prognostic value, although clinical evidences were received not for all of them. Multiple, complementary biomarkers of biomechanical stress and endothelial dysfunction appears to be attractive in this context. CV 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 [83]. Measurement of serum levels of hs-CRP, galectin-3, NPs, and hs-cTnT probably allows the identification of T2DM patients at risk of CV events, although the predictive role of other cardiac biomarkers, i.e., soluble ST2, GDF-15, FGF-23 is not still understood [74,84]. 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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