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**Role of novel biomarkers in diabetic cardiomyopathy**

Kumric M *et al*. Biomarkers in diabetic cardiomyopathy

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**Abstract**

Diabetic cardiomyopathy (DCM) is commonly defined as cardiomyopathy in patients with diabetes mellitus in the absence of coronary artery disease and hypertension. As DCM is now recognized as a cause of substantial morbidity and mortality among patients with diabetes mellitus and clinical diagnosis is still inappropriate, various expert groups struggled to identify a suitable biomarker that will help in the recognition and management of DCM, with little success so far. Hence, we thought it important to address the role of biomarkers that have shown potential in either human or animal studies and which could eventually result in mitigating the poor outcomes of DCM. Among the array of biomarkers we thoroughly analyzed, long noncoding ribonucleic acids, soluble form of suppression of tumorigenicity 2 and galectin-3 seem to be most beneficial for DCM detection, as their plasma/serum levels accurately correlate with the early stages of DCM. The combination of relatively inexpensive and accurate speckle tracking echocardiography with some of the highlighted biomarkers may be a promising screening method for newly diagnosed diabetes mellitus type 2 patients. The purpose of the screening test would be to direct affected patients to more specific confirmation tests. This perspective is in concordance with current guidelines that accentuate the importance of an interdisciplinary team-based approach.

**Key Words:** Diabetic cardiomyopathy; Heart failure; Biomarkers; Diabetes mellitus; Cardiomyopathy

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**Core Tip:** **D**iabetic cardiomyopathy (DCM), which affects 12% of diabetics, is an under-recognized and lethal complication of diabetes. Thus, there is an urgent need for reliable and available biomarkers for DCM detection. To date, none of the conducted studies have been successful in identifying such biomarkers. Hence, in concordance with current guidelines that accentuate the importance of an interdisciplinary team-based approach, we propose the combination of speckle tracking echocardiography and a few novel biomarkers as a screening method for DCM in patients with new onset diabetes mellitus type 2.

**INTRODUCTION**

The first records of diabetic cardiomyopathy (DCM) date back to 1972[1], when it was first observed in the post-mortem analysis of diabetics who died of heart failure (HF), having no evidence of coronary artery pathology or any other pathology that could explain the observed structural changes. These findings were supported by the Framingham study in which HF was five times more common among patients with diabetes mellitus (DM)[2], even after the adjustment for hypertension and coronary heart disease. DCM is now commonly defined as cardiomyopathy in patients with DM in the absence of coronary artery disease, valvular disease, and hypertension, or any other conventional cardiovascular risk factor for that matter[3]. Diagnostic criteria include left ventricular diastolic dysfunction and/or reduced left ventricular ejection fraction, pathological left ventricle hypertrophy and interstitial fibrosis[4]. However, timely and appropriate diagnosis is still fairly challenging in everyday clinical practice[5]. The reason behind the exigent diagnosis of this clinical entity lies in the long asymptomatic phase of the disease. DCM initially presents with clinically covert myocardial fibrosis, dysfunctional cardiac remodeling and associated diastolic dysfunction, later progressing to systolic dysfunction, and eventually to overt HF. The changes that lead to DCM are triggered by hyperinsulinemia and increased insulin resistance, whereas the underlying molecular changes that are involved in the pathophysiologic development of DCM include: Abnormalities in the adenosine monophosphate-activated protein kinase, nuclear factor κ-light-chain-enhancer of activated B cells, nuclear factor erythroid 2–related factor 2, mitogen-activated protein kinase (MAPK), cyclic adenosine 5′-monophosphate-responsive element modulator, peroxisome proliferator-activated receptors (PPARs), O-linked N-acetylglucosamine, protein kinase C (PKC), micro ribonucleic acid (microRNA) and exosome pathways[4]. As DCM is now recognized as a cause of substantial morbidity and mortality among patients with diabetes mellitus, affecting 12% of patients with diabetes, various expert groups struggle to identify a suitable biomarker that will help in the recognition and management of DCM[6,7]. The rising burden of DM, estimated to afflict 592 million people by 2035[8], calls attention to this matter even more. Similarly, the prevalence of DM in HF could be over 40%, while in patients with DM, the prevalence of HF ranges from 10% to 22%[9,10]. Unfortunately, so far none of the conducted studies have resulted in the implementation of either conventional cardiac biomarkers or new diagnostic tools in DCM management, yet the current guidelines accentuate the importance of an interdisciplinary team-based approach[11]. Therefore, in this study we sought to address the role of certain biomarkers that have shown potential in either human or animal studies and which could eventually result in mitigating the poor outcomes of DM by participating in the prevention and/or treatment of DCM.

**Pathophysiology of diabetic cardiomyopathy**

So far, most of the underlying pathophysiological mechanisms leading to DCM have been disclosed[12]. The pathogenesis of DCM is complex and consists of the following systemic and cardiac processes triggered by hyperinsulinemia and increased insulin resistance: impaired coronary microcirculation, dysregulation of the sympathetic nervous system activity and the renin-angiotensin-aldosterone system (RAAS), inappropriate immune response, metabolic disequilibrium of the myocardium and abnormalities of the sub-cellular components. Underlying these pathophysiological events, a role for several proteins and signaling pathways has emerged: adenosine monophosphate-activated protein kinase, PPARs, O-linked N-acetylglucosamine, Sodium-Glucose Cotransporter 2 (SGLT2), PKC, MAPK, NFκB, erythroid 2–related factor 2, microRNA and exosomes[4,13]. Other important mediators implicated in almost every step of DCM development are reactive oxygen species. It is important to point out that these processes are not independent, instead they mutually interact and result in HF. In this review, we highlight some of the above-mentioned pathways relevant for comprehension of the role of biomarkers, as greater details of DCM pathophysiology are beyond the scope of this review. The development of HF in DM is gradual and consists of three distinct phases.

Insulin cell signaling is comprised of two major transduction pathways. The first being phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT) and the other beingMAPK[13]. The PI3K-AKT pathway mainly exerts the metabolic functions of insulin, most important being glucose transporter-4 (GLUT4) cell-surface expression and endothelial nitric oxide (NO) synthase (eNOS) expression. In contrast, the MAPK pathway promotes growth, hypertrophy and remodeling[14]. In an insulin resistant state, these pathways are imbalanced in favor of the MAPK pathway, creating a base for DCM development[15]. Attenuation of the PI3K-AKT and up-regulation of the MAPK pathway are a result of complex interactions between ROS, overfeeding, RAAS activity and many other components which we will discuss further.

Coronary microcirculation seems to be impaired in DM, mediated by multiple pathophysiological processes[16]. Stiffness of small blood vessels is commonly observed among patients with DM, driven by hyperinsulinemia-induced vascular smooth muscle cells differentiation to an osteoblast-like phenotype[17]. In an insulin-resistant state, owing to reduced eNOS levels, NO synthesis is reduced, whereas its degradation is accelerated as a consequence of a heightened state of oxidative stress[18,19]. As it promotes vasodilation *via* guanylyl cyclase activation, a negative balance of NO leads to coronary vasoconstriction[20]. Recent studies suggest a role of the endothelial-to-mesencyhmal transition (EndoMT) in this setting. EndoMT is a mechanistic phenomenon that explains the loss of normal vascular phenotype of endothelial cells, increased cardiac fibroblast content and cardiac fibrosis in the diabetic heart[21]. Importantly, Widyantoro *et al*[22]showed that cardiac fibrosis in the diabetic myocardium is due to stimulation of the EndoMT pathway. It seems that this detrimental cascade which is translated from vasculature onto myocardium could be an important contributor to the onset of HF with preserved ejection fraction (HFpEF)[23].

Altered sympathetic nervous system activity is one of the established hallmarks of DM[24]. The over-expression of β1-adrenergic receptors has been shown to promote myocyte hypertrophy, interstitial fibrosis and myocyte apoptosis[25]. Conversely, sympathetic denervation as a part of  cardiac autonomic neuropathy (CAN) is also an important feature of DM. Interestingly, myocardial regions of persistent sympathetic innervation exhibit the greatest deficits of vasodilator reserve[26], thus indicating an association between CAN and impaired myocardial blood flow.

It has been shown that hyperglycemia increases the transcription of angiotensinogen and angiotensin II (At II) production from the local angiotensin converting enzyme, hence increasing the RAAS activity[27]. Accordingly, obesity is also associated with up-regulation of the RAAS[28]. On the other hand, RAAS activity influences insulin signal transduction pathways on multiple levels, which results in an abundance of cardiac and systemic repercussions[29]. By stimulating the creation of ROS *via* nicotinamide adenine dinucleotide phosphate oxidase, as well as by direct phosphorylation of the insulin receptor substrate-1 serine residues, At II inhibits the metabolic PI3K signaling pathway. As eNOs production is mainly dependent on the PI3K pathway[30], At II reduces NO synthesis and thus promotes endothelial dysfunction of myocardial blood vessels[31]. Additionally, aldosterone activation of the mineralocorticoid receptors results in increased ROS production, increased sodium channel expression and activation of serum/glucocorticoid-regulated kinase 1. Altogether, this leads to reduced production of NO and consequently vascular stiffness and impaired cardiac relaxation[32]. Conversely, the MAPK pathway enhancement by At II and ROS induces vascular remodeling[33].

Low-grade systemic inflammation and increased polarization towards the pro-inflammatory M1 macrophages and TH1 lymphocytes is fairly common among obese patients and in an insulin-resistant state[15,34,35]. Although regulatory T cells attenuate inflammation in the myocardium, it has been proposed that the secreted pro-inflammatory cytokines, chemokines and growth factors could result in increased cardiac fibrosis and impaired diastolic relaxation[36,37].

An influx of glucose to the myocardial cells is mainly exerted *via* insulin-mediated GLUT4, whereas free fatty acids (FFA) uptake depends on fatty acid translocase (CD36) expression[14,38]. Under physiological circumstances, the heart can use both glucose and FFA as a source of energy. However, in an insulin-resistant state, the expression of GLUT4 diminishes, whereas CD36 expression on plasma membrane is up-regulated. Moreover, elevated levels of intracellular FFA stimulate PPAR-alpha expression, which leads to an increased uptake and oxidation of FFA. Hence, myocardial metabolism shifts from glucose to FFA oxidation, making the myocardium less energy-efficient[39]. As DCM progresses, the expression of genes regulating beta-oxidation of fatty acids is down-regulated, thereby further mitigating the metabolic efficiency of the myocardium[40]. Hyperglycemia leads to the accumulation of the advanced glycation end-products (AGE) *via* non-enzymatic glycation. The AGE induce extracellular matrix cross-linking thus promoting myocardial fibrosis and impaired passive relaxation[13]. Additionally, AGE can stimulate a pro-inflammatory state by binding to the receptors for AGE[41,42]. It should be noted that a relatively novel group of anti-diabetic agents, the SGLT2 inhibitors, have been shown to attenuate hyperglycemia-induced cardiac dysfunction in lipodystrophic mice[43]. In concordance, they exert a cardioprotective effect manifested by improved systolic function, decreased fibrosis and reduced inflammation in At II infusion-induced cardiomyopathy in diabetic mice[44], elucidating the beneficial effects of SGLT2 inhibitors observed in human studies[45]. Mechanisms by which SGLT2 inhibition mitigates DCM and HF in general is an increase in natriuresis, osmotic diuresis, plasma volume contraction, reduction of blood pressure and arterial stiffness and lastly, by providing highly energy-efficient substrates for cardiac metabolism, such as β-hydroxybutyrate[43,45].

Mitochondrial damage is one of the pivotal pathophysiological mechanisms that contribute to DCM. Substrate overflow induces mitochondrial ROS production and impaired oxidative phosphorylation. Consequently, this leads to altered mitochondrial Ca2+ handling, which prolongs diastolic relaxation time (diastolic dysfunction) and in later stages leads to cell death[46-48]. Apart from mitochondrial damage, excessive ROS also impair post-translational protein modifications that occur in the endoplasmic reticulum and interfere with insulin signaling pathways. Endoplasmic reticulum stress further stimulates ROS production and favors myocyte apoptosis.

MicroRNAs, small non-coding RNAs, take part in the regulation of mitochondrial function, ROS production, Ca2+ handling, apoptosis, autophagy and fibrosis, all of which are regarded as important mechanisms in diabetes induced HF[13]. These microRNAs are transported in exosomes, recently recognized extracellular vesicles involved in cell-to-cell communication[49].

The development of DCM can be divided in three distinct phases (Figure 1)[13]. In the initial phase, there are no obvious changes in the myocardium tissue and systolic function is preserved[50]. However, using echocardiography and magnetic resonance imaging (MRI) in rodents, authors observed subtle anomalies that indicate impaired diastolic relaxation. MRI findings that pointed to the impaired diastolic relaxation were slow initial and peak filling rates, whereas abnormal myocardial performance index, long period of isovolumic relaxation and impaired septal annular wall motion were the observed echocardiographic diastolic parameters[51,52,15]. In humans, early DCM is characterized by increased cardiac stiffness and impaired cardiac relaxation with consequent reduction in early diastolic filling and an increase in atrial filling[50,53]. In addition, another hallmark is a decrease in the myocardial blood-flow reserve that can be detected by various imaging techniques[54]. Needless to say, the whole initial phase is completely asymptomatic. As underlying pathophysiological mechanisms continue to exhibit their deleterious cellular effects on cardiac tissue, DCM becomes more and more evident. In the advanced phase, as myocardium becomes hypertrophic and increasingly permeated with fibrous tissue, left ventricular mass and wall thickness both increase and hence, diastolic dysfunction becomes clinically apparent. In this phase, patients may notice first symptoms which correspond to the symptoms observed in HFpEF, the most prominent being exercise intolerance[55,56]. In the late phase of DCM development, except for diastolic dysfunction, further progression of cardiac remodeling finally results in mitigation of systolic function and consequent HF with reduced ejection fraction[12]. It is important to note that DCM staging still remains theoretical, since it is difficult to reach a definite diagnosis of DCM. However, we believe that staging is useful because it highlights the importance of timely DCM diagnosis.

**Biomarkers in diabetic cardiomyopathy**

***Role of traditional cardiac biomarkers in the management of diabetic cardiomyopathy***

Established cardiac biomarkers used for detection in patients with HF have failed to timely recognize DCM. Brain natriuretic peptide (BNP) correlation with HF is blunted owing to the association between BNP and insulin resistance[57]. In contrast, N-terminal pro-BNP and ANP have been able to predict HF in experimental DCM rat models[58,59]. Furthermore, both natriuretic peptides successfully demonstrated diastolic dysfunction in diabetics and in conjunction with 2D echocardiography[60,61]. However, their value as a biomarker was limited to symptomatic patients, those with pseudo-normalized mitral flow pattern and those with a restrictive filling pattern[60]. There was no correlation of these natriuretic peptides with diastolic dysfunction among asymptomatic patients and those with relaxation abnormalities. Additional studies also demonstrated a lack of correlation among asymptomatic patients with diastolic dysfunction and overall poor correlation with most of the echocardiography parameters[62,63]. In conclusion, the utility of natriuretic peptides in pre-clinical DCM detection is limited; however, BNP seems to be an independent predictor of poor outcomes in this cardiomyopathy[64-66].

Another family of entrenched cardiac markers are the troponins, a set of proteins that control the calcium-mediated interaction between actin and myosin. This multiprotein complex consists of troponin C which binds calcium, troponin T (TnT) which binds to tropomyosin and troponin I (TnI) which prevents actin-myosin interaction[67]. Cardiac troponin I and T are commonly used in routine clinical practice due to their high sensitivity and specificity for the detection of myocardial injury[68]. Both human and animal studies suggest that TnI and TnT are constitutively phosphorylated in diabetes *via* PKC, leading to depressed myofilament function and Ca2+ responsiveness[69,70]. Of note, losartan, an At II receptor blocker seems to abrogate TnI phosphorylation[71]. Although it is well-known that TnT and TnI are elevated among patients with diabetes, especially among those with concomitant coronary artery disease, to our knowledge no studies have investigated the difference in troponin plasma levels between diabetics with DCM and diabetics without DCM[72,73]. Taken together, established laboratory biomarkers measuring myocardial injury and mechanical hemodynamic overload of the ventricles are not specific markers of DCM.

***Novel biomarkers of diabetic cardiomyopathy***

Cardiotrophin-1 (CT-1), a member of the glycoprotein 130 family, is a potent inducer of cardiomyocyte hypertrophy *in vitro*[74]. CT-1 secretion is stimulated by various triggers: mechanical stretch of cardiomyocytes, hypoxic stress, ROS, At II, aldosterone, urocortin, glucose, insulin and fibroblast growth factor-2[75-82]. Triggered by any of the above-mentioned, CT-1 modulates myocardial contractility, fibrosis and cardiac conduction *via* activation of the JAK/STAT and MAPK pathways (Figure 2)[83,84]. Apart from its effects on heart remodeling, CT-1 also takes part in cardiac glucose metabolism by increasing insulin-stimulated glucose uptake[85,86]. In line with this, plasma CT-1 levels are positively correlated with basal glycemia and left ventricular hypertrophy[87]. Other studies showed elevated plasma levels of CT-1 in recently diagnosed diabetics and neonates exposed to maternal diabetes[88], but interestingly, reduced levels in obese non-diabetics[89,90]. Moreover, low CT-1 plasma levels seem to be associated with decreased risk of both metabolic syndrome and DM type 2 in obese subjects[91]. Although CT-1 is to a great extent implicated in DCM, there are two major setbacks that prevent CT-1 implementation in the DCM diagnostic algorithm[92]. Firstly, CT-1 is also expressed by various tissues such as liver, lung, kidney and skeletal muscle[93]. Secondly, CT-1 plasma level alterations are also associated with other types of cardiomyopathies, including ischemic, making it less specific[84].

Insulin-like growth factor binding protein 7 (IGFBP7) is a part of the IGFBP superfamily of homogenous proteins which regulate the IGF signaling pathway by binding with insulin and IGFs[94]. Unlike IGFBP 1-6, IGFBP7 has low binding affinity to IGF but high affinity to insulin[95]. Owing to its high binding affinity to insulin, IGFB7 may interfere with the biological response of insulin, subsequently inducing insulin resistance and is involved in the development of diabetes, as shown by multiple studies (Figure 2)[96,97]. Apart from its role in insulin signaling, IGFBP7 is associated with multiple processes including fibrogenesis and tumor development[98,99]. IGFBP7 has also been implicated in HF where it serves as a novel prognostic biomarker for heart failure with reduced ejection fraction and shows a significant correlation with the presence and severity of the echocardiographic parameters of abnormal diastolic function[100]. In a recent study, the potential of IGFBP7 in improving the diagnosis of acute HF has been highlighted[101]. The most important evidence of IGFBP7 utility in the setting of DCM was provided by Shaver *et al*[102] who tested the potential of various serum biomarkers in a West Virginian population. The authors compared plasma levels between controls and diabetics (DM group), but more importantly, between diabetics with diastolic dysfunction (DM, DD+ group) and diabetics without diastolic dysfunction (DM, DD- group). IGFBP7 plasma levels were significantly higher in the DM, DD+ group in comparison to the DM, DD- group. Given their role in insulin resistance, fibrogenesis, HF development and the results presented by Shaver *et al*[102], we argue that further research of IGFBP7 in this manner is valuable as it could be a candidate for early detection of DCM.

Another important finding by Shaver *et al*[102] is in regards to transforming growth factor-β (TGF-β), a ubiquitous fibrogenic cytokine that promotes extracellular matrix accumulation[103]. As a result of increased ROS production, TGF-β is up-regulated in patients with diabetes[104]. Additionally, TGF-β correlates with the degree of cardiac fibrosis[105]. Of note, although most of the TGF-β-induced cardiac fibrosis is exerted by modulating the fibroblast phenotype and function[106], an additional mechanism that may contribute to fibrosis is TGF-β-mediated induction of EndoMT[107,108], a deleterious process implicated in HFpEF pathophysiology[23]. Shaver *et al*[102] reported higher plasma levels of TGF-β in patients with both DM and DD in comparison to the other two groups, respectively. Therefore, TGF-β could serve as a marker in DCM management. This is in line with previous studies conducted on this topic. By using FT23, an orally active anti-fibrotic compound, Tan *et al*[109] successfully demonstrated the TGF-β-mediated attenuation of diastolic dysfunction in an experimental model of DCM. In line with the latter, Smad3, a signaling pathway by which TGF-β exerts a part of its pro-fibrotic features, has been shown to mediate diabetic cardiac hypertrophy, fibrosis, and diastolic dysfunction[110,111].

Activin A, a protein secreted by epicardial adipose tissue (EAT) is another member of the TGF-β superfamily that seems to be involved in the development of DCM[112]. Greulich *et al*[113] demonstrated that excessive activation of Activin A-signaling results in contractile dysfunction and insulin resistance in high fat diet fed guinea pigs. The underlying mechanism seems to be inhibition of insulin-mediated phosphorylation of rrAkt, a key regulator of myocardial glucose uptake (Figure 2)[114]. In addition, authors also observed decreased calcium ATPase-2a expression and sarcomere shortening. By cultivating rat cardiomyocytes with EAT byoptates derived from diabetics, Blumensatt *et al*[115] highlighted the role of microRNA in Activin A-induced insulin inhibition and led to further disclosure of DCM pathophysiology. Finally, the potential of Activin A as a biomarker in diabetes has been exploited by Chen *et al*[116]. These authors reported an association between Activin A plasma levels and both impaired myocardial glucose metabolism and left ventricular remodeling in patients with uncomplicated type II diabetes[116]. In contrast to diastolic dysfunction and HF, Activin A is not elevated in uncomplicated DM, which could be beneficial for its utility as a biomarker. However, we doubt that Activin A will find clinical implications in this manner, as its plasma levels are affected by metformin, a ubiquitous diabetes medication, and the secretion of Activin A is not limited to EAT but it is also expressed by many other cells[116-121].

Considering the importance of ROS overproduction in DCM pathophysiology and the well-known ROS-induced inflammatory response, multiple authors have tested the potential of inflammatory markers in this setting. A recent study on core gene biomarkers in patients with DCM addressed the vital role of interleukin-6 in DCM pathophysiology[122]. Furthermore, Shaver *et al*[102] found that both interleukin-6 and tumor necrosis factor-alpha are more increased in patients with both DM and DD in contrast to patients with DM exclusively. Nevertheless, owing to the low specificity of the two, it seems that growth differentiation factor-15 (GDF-15), another inflammatory marker, has a much better chance of being implemented in DCM diagnosis[123]. GDF-15, another member of the TGF-β superfamily is produced in response to oxidative stress and inflammation by multiple cell types, including macrophages, adipocytes, and cardiovascular cells[123]. Elevated plasma levels of GDF-15 seem to be associated with increased risk in fatal and non-fatal cardiovascular events of community-dwelling subjects and patients with cardiovascular disease, as shown by multiple studies[125-127]. Interestingly, in these studies GDF-15 levels were higher among patients with established DM type 2. Additionally, several studies addressed the contribution of GDF-15 in diastolic dysfunction[128,129]. As demonstrated by Dominguez-Rodriguez *et al*[130], elevated levels of GDF-15 can predict DCM development in the absence of other risk factors, such as age, smoking, hypertension and known cardiovascular disease. Importantly, multiple authors have shown that GDF-15 expression in various tissues is higher in pre-diabetes and DM type 2 patients in comparison to individuals without the mentioned metabolic disorders, making GDF-15 a promising biomarker for identification of DCM and its repercussions among diabetics[131,132]. Notably, a new class of GFRAL (high affinity binding receptor for GDF-15)/RET (receptor tyrosine kinase)-based drugs for the treatment of obesity and metabolic syndrome could improve cardiovascular risk in individuals with metabolic diseases by mediating the endogenous effects of GDF-15[133].

Galectin-3 is a lectin family protein that has been associated with fibrosis and inflammation in cardiac, kidney and liver diseases[134,135]. Galectin-3 levels correlate with accumulation of AGE, oxidative stress products and pro-apoptotic pathways which directly promote endothelial dysfunction[136,137]. Perhaps the most important role of galectin-3 is its role in HF, where galectin-3 is an important mediator by which multiple molecules, such as At II and aldosterone, exert their pro-fibrotic activity and where it is able to promote oxidative stress with well-known repercussions[138-143]. The first evidence to support these findings were provided by Sharma *et al*[144] in a study which demonstrated that galectin-3 was the strongest differentially regulated gene associated with HF. Subsequently, a number of authors produced abundant evidence that successfully associated galectin-3 with HF in both animal models and in human studies, leading to the Food and Drug Administration approval of galectin-3 as a novel biomarker for predicting cardiovascular adverse events in 2010[145-149]. It is important to note that inhibition of galectin-3 could be an important target molecule in the HF therapeutic approach, based on its potential to undermine cardiac fibrosis and mitigate poor outcomes of HF. Multiple studies have highlighted the link between DM type 2 and galectin-3. The Dallas Heart Study associated galectin-3 with diabetes prevalence and incidence even after adjustment for conventional metabolic and cardiovascular risk factors[150]. Furthermore, in young obese patients without known cardiovascular disease, galectin-3 is associated with the presence of left ventricular diastolic dysfunction and elevated pulmonary artery systolic pressure, indicating its possible role in screening for preclinical metabolic heart disease[151]. On the other hand, in patients with HF, galectin-3 plasma levels were higher among those with impaired glucose metabolism (Figure 2)[152]. Finally, the possible role of galectin-3 in the DCM diagnostic approach was evaluated in a recent study by Flores-Ramírez *et al*[153]. The study showed that galectin-3 is elevated in diabetic patients with mild depressed ejection fraction and is associated with a diminished global longitudinal strain, an easy and reproducible echocardiographic tool in the evaluation and follow-up of DCM[154].

The soluble form of suppression of tumorigenicity 2 (sST2) is a interleukin-33 (IL-33) decoy receptor that tones down the Th2 inflammatory response *via* the IL-33/ST2/sST2 axis (Figure 3)[155]. Consequently, the protective effects of IL-33 in atherosclerosis and cardiac remodeling are mitigated, as this axis is an important component of the autocrine/paracrine mechanism that prevents tissue injury[156,157]. Increased plasma concentrations of sST2 are not specific for a single disorder in humans which undermines its value as a biomarker[158]. However, increased plasma levels of sST2 have been linked to a worse prognosis in numerous diseases, the most important being HF[159-162]. In line with this, sST2 is now included in the 2017 ACCF/AHA guidelines for additive risk stratification of patients with acute and chronic HF[163]. In the case of diabetes, Fousteris *et al*[164] demonstrated higher plasma concentrations of sST2 among patients with DM type 2 in comparison to healthy controls. More importantly, authors observed even higher levels of sST2 in patients with both DM type 2 and grade I left ventricular diastolic dysfunction, an early finding in DCM[165]. The presented data suggest a possible association between sST2 and the early stages of DCM; however, a larger body of evidence is needed to support these findings.

Long noncoding RNAs (lncRNAs) are a diverse subgroup of noncoding RNAs comprised of sequences longer than 200 nucleotides that act as epigenetic regulators of gene expression[166]. There is a large body of evidence indicating that lncRNAs are implicated in cardiac development, function and diseases[167,168]. Recent studies suggest that circulating lncRNAs could serve as diagnostic and prognostic biomarkers of cardiac remodeling and survival in cardiovascular diseases[169,170]. Both *in vitro* and *in vivo* studies showed that lncRNAs are involved in the pathophysiology of diabetes and its complications[171-173]. The most important study that addressed the potential of multiple lncRNAs as early DCM biomarkers was conducted by de Gonzalo-Calvo *et al*[174]. These authors compared a panel of lncRNAs that are directly involved in either diabetic conditions or cardiovascular disease and attempted to determine their relationship with MRI indices of cardiac dimensions and function. Long intergenic non-coding RNA predicting cardiac remodeling (LIPCAR) was inversely associated with E/A peak flow, an established indicator of diastolic dysfunction. In addition, LIPCAR serum levels positively correlated with grade I diastolic dysfunction. However, although LIPCAR was also correlated with waist circumference, plasma fasting insulin, subcutaneous fat volume and HDL-C, which could seemingly undermine LIPCAR value as a specific biomarker of cardiac impairment, the observed correlation with cardiac dysfunction was independent of the aforementioned. On the other hand, smooth muscle and endothelial cell-enriched migration/differentiation-associated long noncoding RNA (SENCR) and myocardial infarction-associated transcript (MIAT) lncRNAs serum levels were both associated with left ventricular mass to volume ratio, a marker of cardiac remodeling, even after adjustment for possible confounding factors. Notably, the highest left ventricular mass to volume ratios were observed in patients with the highest MIAT and SENCR expression. It is also important to point out that neither SENCR nor MIAT levels correlated with other clinical, biochemical, or metabolic parameters, which supports the hypothesized utility of these lncRNAs as biomarkers of left ventricular remodeling.

MicroRNAs are small noncoding RNA molecules which regulate gene expression by post-transcriptional mechanisms[175]. These molecules control around 30% of all protein-coding genes of the mammalian genome[176]. Additionally, microRNAs are also paracrine mediators of cell-to-cell communication transported *via* exosomes, a mechanism which has lately become an emerging research field for understanding the development of cardiac pathology[177]. The release of circulating exosomes filled with microRNA in the bloodstream from cardiomyocytes, driven by oxidative stress or hypoxia/reoxygenation, as well as stable microRNA-protein complex transport, makes microRNA an attractive target for analytical studies[178-182]. Recent pre-clinical level studies identified several distinct microRNAs which have been involved in DCM pathophysiology. Among many, we highlighted those we thought most suitable for DCM diagnosis based on their pathophysiologic role in DCM: microRNA-223 which regulates Glut4 receptor expression and cardiomyocyte glucose uptake and microRNA-133a which is implicated in cardiac hypertrophy and myocardial matrix remodeling[183-185]. Despite their potential, there are currently no ongoing clinical trials regarding the role of microRNAs in this manner. Perhaps the biggest setback in using microRNAs as markers is discordance between human and animal serum microRNAs associated with DCM[186]. The only exceptions are microRNA-34a, a regulator of high glucose-induced apoptosis and microRNA-30d, a molecule involved in the process of cardiomyocyte pyroptosis[187,188].

**CONCLUSION**

Despite substantial efforts to establish appropriate diagnostic biomarkers of DCM, this entity is not even diagnosed among clinicians, mainly due to the absence of agreement among experts[4]. Hence, new strategies must be applied in order to ameliorate poor outcomes of diabetes-related HF. In an ideal setting, DCM would be recognized in the early asymptomatic phase, before irreversible myocardial damage occurs. Different imaging approaches such as Phase-MRI, Speckle tracking echocardiography (STE) and nuclear imaging have been successful in the recognition of early metabolic myocardial changes in both animal and human studies[189-194]. However, most of these are limited by price and availability, whereas STE, although promising, can have reduced accuracy in irregular ventricular remodeling and wall thinning[6]. Importantly, global longitudinal strain, an echocardiographic measurement, seems to be more impaired in DM *vs* healthy controls whereas among diabetics, it is more impaired in patients with albuminuria in comparison to patients without it[195]. In addition, patients with uncomplicated DM type II show a similar time-dependent pattern of global longitudinal strain change, altogether indicating subclinical systolic dysfunction in patients with diabetes that is associated with duration and extent of the disease[196]. Of the aforementioned biomarkers, we believe that lncRNA, sST2 and galectin-3 will be the most beneficial for DCM detection, as their plasma/serum levels accurately correlate with the early stages of DCM.

In addition, there are several molecules which are rarely debated in this manner and which we find valuable for further research based on their functional properties. Catestatin, a pleiotropic cardioprotective peptide that counterbalances the negative effects of the sympathetic nervous system, is implicated in both the metabolic syndrome and HF[197-199]. Specifically, alongside sST2, our recent study suggested that catestatin plasma levels reflect myocardial fibrosis and sympathetic overactivity during the acute worsening of HF[200,201]. With regard to diabetes, catestatin has been shown to increase glucose uptake and up-regulate GLUT4 plasma expression in rat cardiomyocytes[202], as well as improve insulin sensitivity in mice with diet-induced obesity[203]. Apelin, a physiologic antagonist of RAAS, has been shown to orchestrate complex tissue-specific control of cardiomyocyte hypertrophy and, more importantly, to attenuate the development of DCM by preventing mitochondrial dysfunction[204-206].

To sum up, further research is needed to improve DCM approach strategies. The combination of relatively inexpensive and accurate STE with some of the highlighted biomarkers seems promising (Table 1); however, well-designed studies with long-term follow-up and validation are obligatory for implementation in everyday clinical practice. With the exception of “What to test?”, rather more important questions are “When and whom to test”. Given that DCM affects around 12% of diabetics, we need a predictive scoring system to establish that a patient is at risk of DCM development, as they all are. Thus, screening methods should be applied for all newly-diagnosed type 2 DM patients. In DM type 1, due to the discrepancy in certain pathophysiological aspects in respect to DM type 2, further research is needed to reach proper conclusions[207,208]. With regard to “When to test?”, as DCM progression deteriorates heart function stepwise and as new therapeutic strategies that specifically target early phase mechanisms emerge, it will be vital to detect DCM as soon as possible. Finally, we argue that an effort must be made to create an easy and reproducible algorithm which will, by using a combination of STE and biomarkers, direct affected patients to confirmation tests such as Phase-MRI. Consequently, in patients with validated DCM, new specific therapies that target early phase mechanisms could be applied. This type of approach is needed to stratify patients because most of the new therapies will be very costly.

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**Footnotes**

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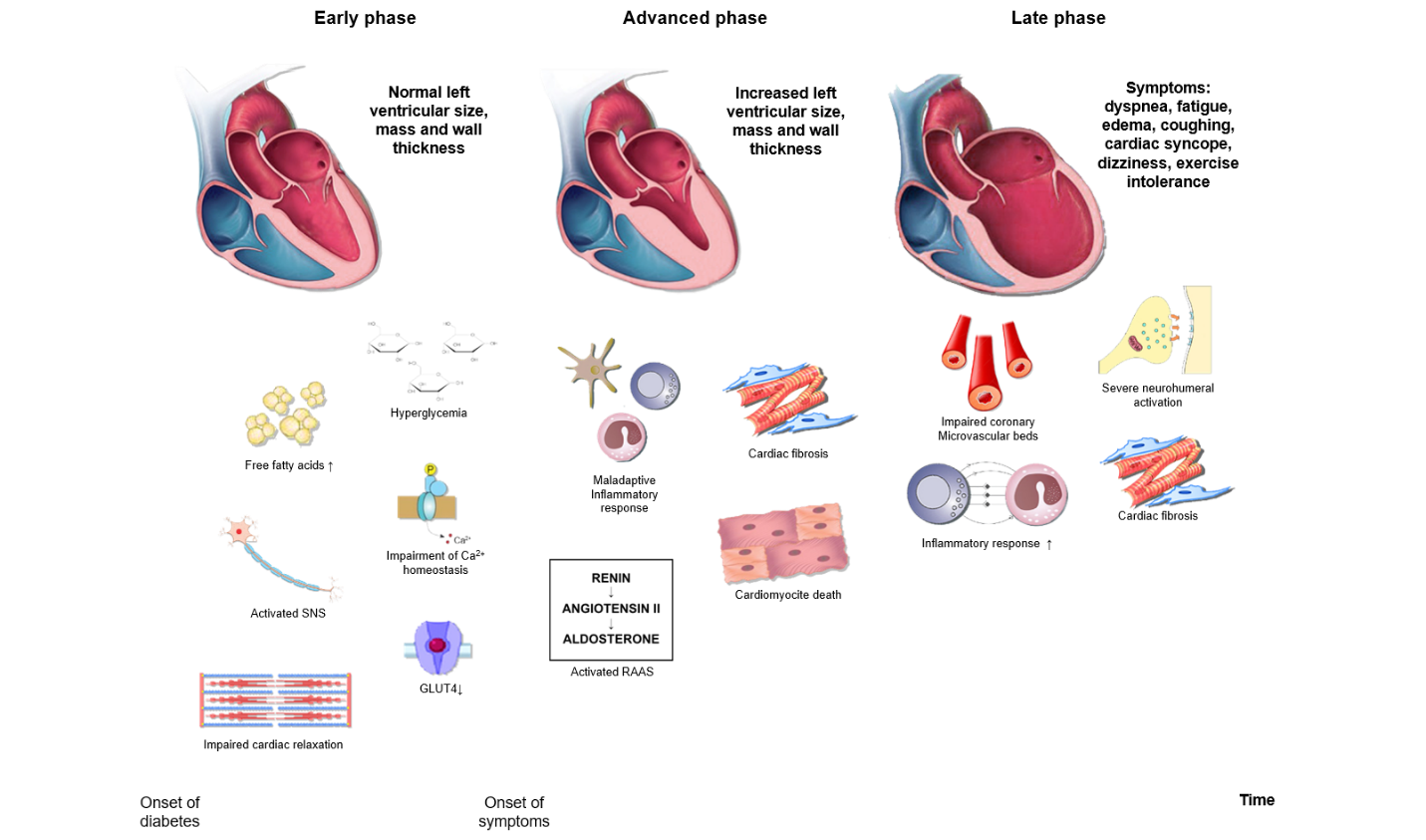
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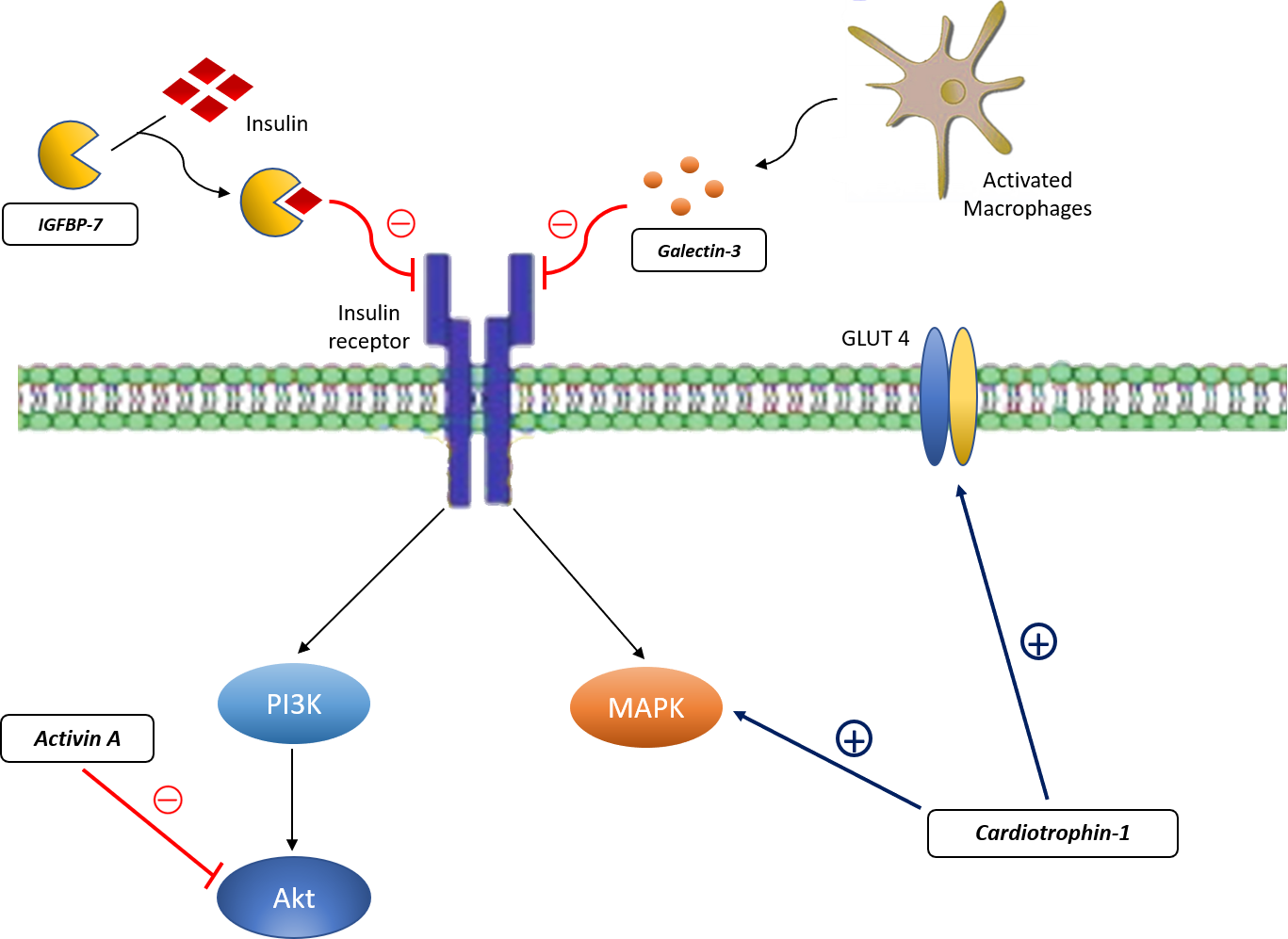
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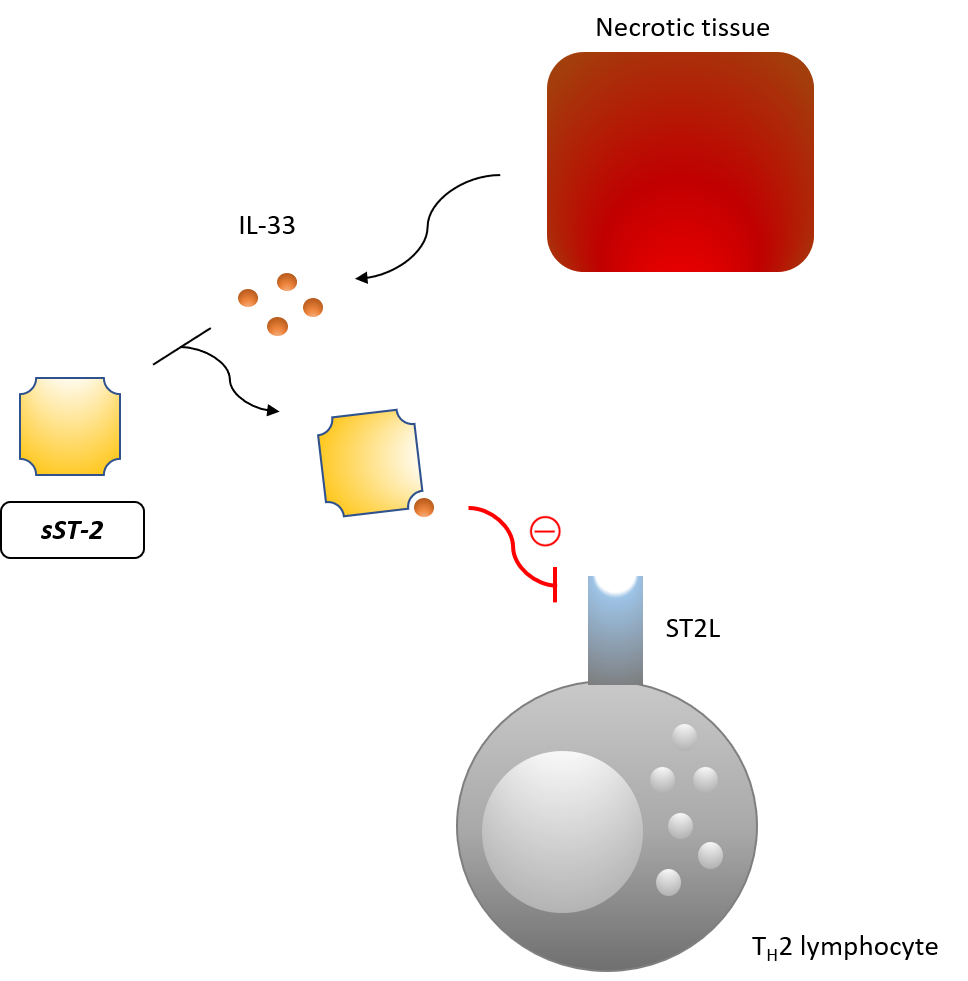
**Figure Legends**



**Figure 1 Schematic representation of the diabetic cardiomyopathy phases**. Each background color corresponds to its respective phase: green (early phase), yellow (advanced phase), red (late phase). The red line represents the incremental nature of symptom severity. SNS: Sympathetic nervous system; GLUT4: Glucose transporter type 4; RAAS: Renin-Angiotensin-Aldosterone System.

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**Figure 2 Molecular targets of the diabetic cardiomyopathy biomarkers in cardiomyoctes.** MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol 3-kinase-protein kinase B; IGFBP7: Insulin-like growth factor binding protein 7; GLUT4: Glucose transporter type 4.

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**Figure 3 Molecular target of the soluble form of suppression of tumorigenicity 2.** sST2:Soluble form of suppression of tumorigenicity 2; IL-33: Interleukin-33; ST2L: Suppression of tumorigenicity 2 ligand; TH2: T helper lymphocyte type 2.

**Table 1 Promising novel biomarkers in diagnostic approach to diabetic cardiomyopathy**

|  |  |  |
| --- | --- | --- |
| **Biomarker** | **Pathophysiological pathway** | **Supporting evidence** |
| LncRNA (LIPCAR, MIAT, SENCR) | Epigenetic regulation of multiple genes involved in diabetes and cardiac dysfunction | Liu *et al*[171]; Yan *et al*[172]; Carter *et al*[173]; de Gonzalo-Calvo *et al*[174] |
| sST-2 | IL-33 decoy receptor that tones down Th2 inflammatory response *via* the IL-33/ST2/sST2 axis | Fousteris *et al*[164]; Kiencke *et al*[165] |
| TGF-β | The main pro-fibrotic factor in heart failure: it modulates the fibroblast phenotype and function and mediates induction of EndoMT | Shaver *et al*[102]; Iglesias-De La Cruz *et al*[104]; Asbun *et al*[105] |
| Galectin-3 | Mediator by which multiple molecules (*e.g.* angiotensin II and aldosterone) exert their pro-fibrotic activity and promote oxidative stress | Ho *et al*[146]; Ueland *et al*[147]; Sharma *et al*[148] |
| GDF-15 | Regulator of inflammatory pathways involved in regulation of apoptosis, cell repair and cell growth | Berezin[123]; Dominguez-Rodriguez *et al*[130] |

RNA: Ribonucleic acid; LncRNA: Long noncoding ribonucleic acid; LIPCAR: Long intergenic non-coding ribonucleic acid predicting cardiac remodeling; MIAT: Myocardial infarction-associated transcript; SENCR: Smooth muscle and endothelial cell-enriched migration/differentiation-associated long noncoding ribonucleic acid; sST2: Soluble form of suppression of tumorigenicity 2; GDF-15: Growth differentiation factor-15; TGF-β: Transforming growth factor-β; EndoMT: Endothelial-mesenchymal transition.