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Review Article

Potential Biomarkers as Early Detection of Diabetic Cardiomyopathy

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ABSTRACT

Diabetes mellitus (DM) is one of the most prevalent and burdensome among chronic disease worldwide. Its complications accelerate mortality rate within population. Diabetic cardiomyopathy (DCM) is one of diabetes macrovascular complications, which symptoms are frequently unforeseen. Advances in pathogenesis understanding DCM underlying mechanisms remain not fully perceived. Current diagnostic approach of DCM can hardly determine diabetic patients with asymptomatic cardiomyopathy. Previous studies suggested biomarkers might detect early stage DCM. There are numerous selective biomarkers representing several pathophysiological pathways, such as myocardial fibrosis, inflammatory response, cardiomyocyte apoptosis, and metabolic dysregulation in the development of diabetic heart anomaly. It was also reported those biomarkers are useful for the prognostic assessment of the disease. However, not all biomarkers are cardiac specific and can be an auspicious diagnostic tool candidate. Recent studies show that there are certain biomarkers, such as microRNA, H-FABP, IGFBP7, and some other novel cardiac biomarkers were more specifically associated with the pathological mechanism of DCM. In this review, we aimed to discuss the role of several potential cardiac biomarkers as early detection in DCM that may predict future incident of DCM, and contribute to improving mortality prediction in patients with subclinical DCM.

Introduction

Shifting paradigm from communicable disease to non-communicable disease has been leading the physicians to face a substitute challenging maladies burden. One of the arduous cases to cope is Diabetes Mellitus (DM), which the prevalence is steadily increased by years as well as its complication rate. Diabetic heart disease is an important public health risk, comprehended by the fact that one-third of mortality causes in diabetic patients are due to cardiovascular diseases. [1-2]

Diabetes impacts cardiac disorders in various ways, chiefly studied are coronary artery disease (CAD) due to accelerated atherosclerosis, cardiac autonomic neuropathy and diabetic cardiomyopathy (DCM) [3]. DCM is defined by the subsistence of myocardial structure abnormality and physiological dysfunction in the absence of other risk factors, such as CAD, hypertension, carditis, and valvular disease, in individual with DM [4]. Prior study hypothesized etiology of DCM involving intracellular lipid accumulation, altered cell signaling, advanced

glycation end-products (AGEs), and Reactive Oxygen Species (ROS). [5]

Diabetic patients typically carry low-key symptoms with unexpected ongoing complications. It also refers in early stage DCM patients with only diastolic dysfunction owing normal ejection fraction (EF) who rarely show clinical manifestation unless they reach systolic dysfunction in late stage [1]. Current diagnostic approach used to assess DCM is through imaging studies, such as echocardiography and MRI. These tools often used by internist or cardiologist. The lack of screening tools in establishing a definite diagnosis of DCM causes late therapeutic action. This could lead patient ended up in heart failure (HF) state. [6]

Recent studies investigated less invasive, more specific, and sensitive tools to detect subclinical DCM. Biological markers related to DCM are being widely investigated recently. There are numerous novel biomarkers, which involved in DCM underlying mechanisms at the molecular level, such as microRNA, Galectin-3, and fibroblast growth factor 21 (FGF21). Each biomarker has important role in pathophysiology of DCM and may benefit in diabetic related heart disease early diagnostic. In this review, authors aimed to determine the potential biomarkers in early detection of DCM.

Discussion

1. Molecular Mechanism Underlying Diabetic Cardiomyopathy

Early progress of diabetic cardiomyopathy (DCM) is usually asymptomatic and characterized by increased fibrosis tissue and myocardial stiffness. In this state, early diastolic filling begin to decrease, cause impaired atrial filling and enlargement, as well as an elevated LV end-diastolic pressure.

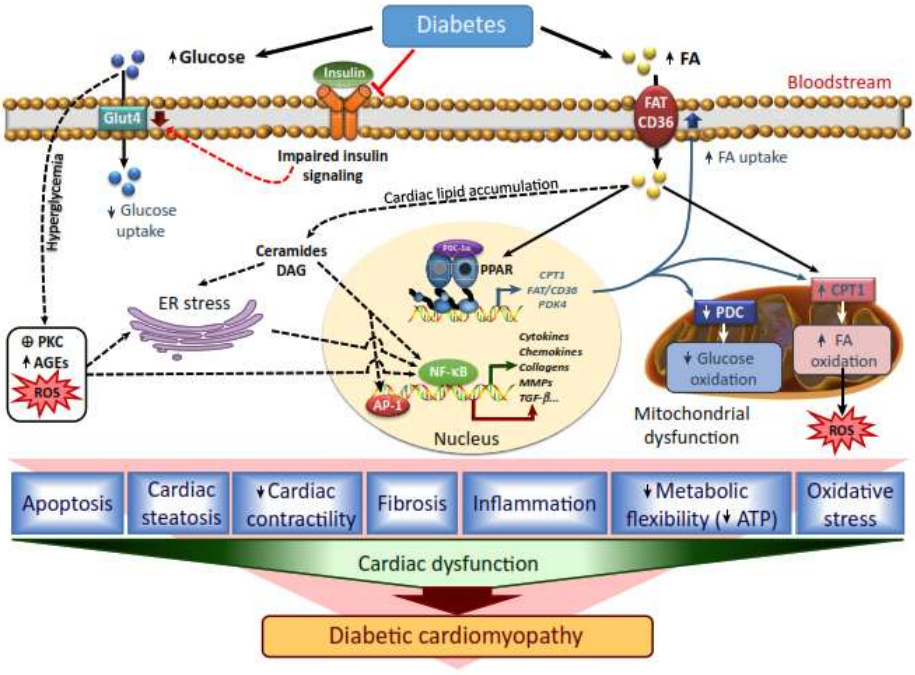

Figure 1. Molecular pathophysiology mechanism underlies diabetic cardiomyopathy.[7]

The pathophysiology mechanism underlies diabetic cardiomyopathy could be seen in Figure 1 [7]. Diabetes increases glucose level and Fatty Acid (FA) level in plasma, which signaling into cardiomyocytes via glucose transporter 4 (GLUT4) and Fatty Acid Translocase (FAT). Upregulated FA activates peroxisome proliferator-activated receptor (PPAR), leading to increased FA uptake and decreased glucose oxidation. Thus, results in mitochondrial dysfunction and ROS production stimulation. By contrast, downregulated insulin signaling pathway due to insulin resistance prevents GLUT4 translocation. Then this process lowers glucose uptake and also induce substrate shift toward increased mitochondrial FA oxidation. Along with increased FA oxidation rate, myocardial lipid accumulation occurs and contributes in the development of HF. Lipid accumulation activates NF-κβ and activator protein-1 (AP-1) transcription factors, resulted in endoplasmic reticulum (ER) stress and mitochondrial degeneration. Furthermore, hyperglycemia stimulates AGEs and ROS production within cardiomyocytes, which trigger local inflammation and interstitial fibrosis. Ultimately, persisted condition leads to cardiac dysfunction. [7]

Underlying familiar pathological factors in the development of DCM are multifactorial [8]. Recent theories stated that metabolic dysregulation has essential role in DCM progressivity. Cardiac metabolism is mainly regulated by peroxisome proliferator-activated receptor (PPAR) gene in biomolecular level [9]. The gene target of PPAR is pyruvate dehydrogenase kinase 4 (PDK4) which encodes the enzyme that catalyze glucose oxidation and is chronically elevated in the diabetic heart. In addition, the uptake activity of FA and glucose in cardiomyocyte is also transcriptionally regulated by PPAR. Under diabetic state, despite the higher FA oxidation rate, myocardial lipid accumulation is a paramount of diabetic heart and ultimately catalyze DCM development [10-11]. It is also characterized by Nf-κB activation, augmented ER stress and mitochondrial dysfunction, which are linked to myocardial injury. [12]

Activation of Nf-κB brought by high level of FFA and hyperglycemic condition in cardiomyocyte results in increased of the expression of cytokines and chemokines, which are involved in the pathophysiology of DCM [12-13]. Besides, insulin resistance also generates the formation of AGEs in cardiac cell, thus altering general gene expression in cardiomyocytes. AGEs also induce collagen formation and elicit a the α myosin heavy chain isoform change. It may induce myocardial fibrosis and early LV diastolic dysfunction. [14]

Hyperglycemia promotes ROS accumulation in cardiomyocytes that lead to increased oxidative stress. Overexpression of ROS generates pro-inflammatory cytokines via upregulation of extracellular signal-regulated protein kinase (ERK) pathway. ROS ultimately induces cardiomyocytes damage, which is commonly observed in the diabetic patients myocardium or animal models [14-15]. From this pathophysiological mechanism, include metabolic dysregulation, systemic and cardiac inflammation, fibrosis, oxidative stress, and cardiomyocyte apoptosis, there are numerous underlying biomarkers which are involved in development of DCM. Others biomarkers involved will be explained further below.

2. Biomarkers as Diagnostic Approach in Diabetic Cardiomyopathy

1.1 Galectin-3

Galectin-3 (Gal3) is a part of ß-galactoside-binding, encoded by LGALS3 gene and weighs 30 kDa [16-17]. Gal3 is well-expressed in epithelial cells, immune cells, endothelial cells and neurons. Gal3

lives in dual cell environment regulated its particular functions [17-18]. Extracellular Gal3 interacts with the ß-galactoside residue of several extracellular matrix (ECM) and cell surface glycoproteins, while intracellular Gal3 acts as a pre-mRNA splicing factor and regulates the cell cycle. Specific localization of Gal3 has abundant roles such as in cell proliferation, macrophage chemotaxis, oxidative stress, apoptosis, angiogenesis, fibrogenesis, and associated in developing insulin resistance as a hallmark of DM. [16,19]

In diabetic patient, Gal3 modulates adipogenesis by stimulating differentiation of preadipocytes into mature adipocytes. It plays a role in the storage capacity of the adipose tissue and associated with derangement of glucose metabolism [20-21]. Moreover, DM induces systemic chronic inflammation, then stimulating pro-inflammatory cells expressing Gal3, which exerts its insulin desensitizing effects by binding to the insulin receptor (IR) at damaged site in a specific organ cell, such as hepatocytes, adipocytes, and cardiomyocytes. Furthermore, it leads to impairment of cell-insulin signaling pathway. As on the heart, increased expression of Gal3 in diabetic patients causes cardiac insulin signaling pathway disruption. This could later promote degradation of cardiomyocyte glucose uptake and ATP. This condition enhances ROS and mitochondrial dysfunction which eventually impairs cardiomyocyte metabolism, alter its structure and functions additionally. [20]

The amenable mechanism of early heart structural and physiological evolution in diabetic patients is cardiac fibrosis and Gal3. It is renowned as an emerging pro-fibrotic actor that leads to tissue fibrosis and remodeling, later cause cardiac hypertrophy. Chronic inflammation in diabetic patients will trigger cardiac fibroblast differentiation as a feedback to fix cell injury. The differentiation invigorates cardiac myofibroblast activation and starts the synthesis of individual pro-collagen chains. This process then induces collagen maturation, resulted in cardiomyopathy-related pathogenesis (myocardial fibrosis, cardiac remodeling and LV dysfunction [22-23]. Consequently, Gal3 is considered as a promising novel biomarker in diabetic patients, especially those with subclinical cardiomyopathy and normal EF.

Compelling evidences recommended Gal3 as a potential biomarker to detect asymptomatic DCM was demonstrated in previous several studies. It is reported that role of Gal3 as DCM screening resulted in significantly escalated Gal3 level in T2DM patients, and it was associated to risen NT-proBNP and cardiac troponin T level [24]. Clinical experiment to understand the impact of Gal3 levels on the progression of structural-functional changes in the myocardium and vessels showed that the levels of Gal3 in the T2DM patients were higher than other group in absence of diabetes. This explained there was a positive correlation between the level of Gal3, insulin resistance and structural-functional cardiac remodeling. Studies in diabetic patients with preserved ejection fraction (pEF) showed that Gal3 had sensitivity and specificity of 94.3% and 65.1% respectively to diagnose patient with pEF heart failure [25]. Either independently or simultaneously with other diagnostic approach, Gal3 is considered as a potential biomarker, which less invasive, to investigate the progressivity of DCM.

1.2 Fibroblast Growth Factor 21

Fibroblast growth factor 21 (FGF21) is a secreted protein which functions as a metabolic regulator, insulin sensitivity, and ketogenesis [26]. Regulation of FGF21 expression on the cell is controlled by peroxisome proliferator-activated receptor-γ (PPAR-γ). It is released into blood by hepatocytes, brown

adipose tissue and skeletal muscle [27-28]. FGF21 requires some receptors (mainly FGFR1 and FGFR4) and β-klotho to perform its roles. [27]

The heart itself was actually not considered an FGF21 main target or source, intriguingly, recent studies demonstrated that FG21 involves in regulating cardiac metabolic function thus supporting cardiac remodeling [26]. This phenomenon occurs in response to cardiac stress stimuli, where cardiac cells induces FG21 expression and activates pro-inflammatory markers in correlation with lowered PPAR-γ co-activator-1 α (PGC1α), a transcriptional co-activator involved in energy metabolism, and oxidative stress control in heart [29]. By all means, FGF21 existence show inhibitory effect on cardiac inflammation and hypertrophy. It is correlated with the induction of PGC1α also as a biomarker which represent threatening ongoing cardiomyoctes damage.

In DCM, FGF21 conducted anti-hyperglychemic and anti-hyperlipidemic action in diabetic mice models. Besides, it was considered that FGF21 inhibition could elevate plasma glucose level and accelerated development of DCM. FGF21 inhibition in DCM mice models also upregulate CD36, a lipid transport protein, resulting in increased lipid concentration, elevated lipid accumulation, and tempting to invoke cardiac hypertrophy and remodeling [30-31]. Plasma FGF21 levels have been correlated to a higher risk of cardiovascular events in diabetic patient [32-33]. In population studies, it was found that increased plasma FGF21 levels predicted the development of T2DM and were independently associated with other pathological change such as atherosclerosis or nephropathy. [34]

Cardiomyopathy is a late consequence of cardiac response to insulin resistance in diabetic patient through myocardial apoptosis. In this case, FGF21 could prevent cardiac apoptosis by activating the ERK-p38MAPK-AMPK pathways in diabetic state. Therefore these data point to FGF21 as key regulator of cardiac metabolism and a potential tool in the strategy development of DCM prevention [35–37]. Clinical study conducted by Ong K et al. DM subjects showed there was elevated baseline serum level of FGF21 were found to be related with a higher risk for cardiac events in diabetic patients. So it is considered if FGF21 could be a potential marker for early detection of cardiometabolic risk.[38]

Serum FGF21 levels were compared between prediabetic, diabetic, and healthy in a recent cross-sectional study. The study showed that serum FGF21 levels were significantly increased in those two first groups. The cut off value for the diagnosis of T2DM in this material had sensitivity and specificity of 82.5% and 60%, respectively [39]. Although the specificity of this biomarker examination still low, this marker may benefit in early DCM screening.

1.3 Heart-type fatty acid-binding protein

Heart-type fatty acid-binding protein (H-FABP) is a protein in myocardium that functions in citric acid cycle. It transports the hydrophobic long-chain fatty acids from cell membrane to mitochondria. [40]

In the study of diabetic rat model, it was investigated that heart containing H-FABP levels is elevated and caused faster consumption in the diabetic cardiomyocytes. H-FABP is a small soluble protein which release more rapidly into circulation in response to the damage of cardiomyocytes compared to cardiac troponin [41–43]. It also showed that H-FABP is important in determination of low-level myocardial injury in prediabetic state [44]. Prior study showed that elevated H-FABP levels related to insulin resistance, systolic dysfunction, myocardial infarction, or HF. Akbal et al. observed that H-FABP was increasing in early cardiac injury

of T2DM patients and also associated in cardiac insulin resistance severity in T2DM [45,46].

Komamura et al. observed that H-FABP may act as a prognostic marker in patients with non-ischaemic dilated cardiomyopathy [47]. Previous study has reported that there is correlation between H-FABP concentration and heart failure severity [48]. Increased serum concentrations of H-FABP can predict the long-term risk of critical cardiac events compared to brain natriuretic peptide (BNP), regardless of the underlying causes. H-FABP provides additional information for prognosis and management in diabetic cardiomyopathy patient. The worse prognosis shown by elevated H-FABP concentrations and BNP, reflecting myocardial membrane damage and increased ventricular filling pressure [47]. This shows that H-FABP may be a potential biomarker to predict the development of DCM.

1.4 Insulin-like growth factor-binding proteins

Insulin-like growth factor-binding proteins (IGFBP7) is a member of the IGFBP family, produced by tissues and organs, including the lung, brain, prostate, bladder, colon, and liver. The insulin growth factor axis modulates in the differentiation, growth, and proliferation of cells. There are 2 growth factors that recently found, these are IGF-I and IGF-II. Each growth factor has specific receptor. IGFBPs bind to IGFs, subsequently limiting IGF access to IGF-I receptors and inhibit activity of IGF. IGFBP7 has a little C-terminus and hundred times lower affinity for IGF-I than other family member. Therefore, IGFBP7 might modulating cell proliferation, angiogenesis, differentiation, cell adhesion, and cellular senescence in a various cells. [49-50]

Decreased glucose transporters (GLUT), particularly GLUT1 and GLUT4 lead to insulin sensitivity impairment and glucose assimilation in cardiomyoctes. Consequently, the glucose cannot assimilate to cardiomyocytes appropriately, in order producing glucose metabolites. Therefore, cardiomyocytes increase fatty acid transporters in response to the lack energy in cell metabolism necessity. Fatty acid could saturate ß-oxidation that collected in the cytosol, subsequently increase ROS production. It affects interstitial fibrosis and IGFBP7 level [51-52]. Hence, IGFBP7 levels correlated with insulin resistance.

Recent study showed that increased IGFBP7 might bind insulin serum. This binding diminishes free insulin level in serum, disturb the binding of insulin in cell surface, and reduce insulin biological effect. It subsequently affects in insulin resistance [49-50]. Furthermore, preclinical study showed that IGFBP7 overexpression in r1-IGFBP-rP1-treated mice significantly increase the production of TGF- ß1, collagen, and fibronectin [53]. In addition, IGFBP7 has role in increasing fibrosis and cardiac hypertrophy in diabetes by modulating insulin receptor activity signaling pathway. It causes cardiac stiffness that leads to diastolic dysfunction [49,54,55]. It shows that alteration of IGFBP7 concentration could be potential cardiac biomarker for DCM because its early arise in asymptomatic DCM and correlation with diastolic dysfunction degree, which describe cardiac stiffness due to fibrogenesis activity.

1.5 Matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP)

Matrix metalloproteinases (MMP) is one of the proteolytic enzymes. It is induced by inflammatory signals to mediate change in extracellular matrix. MMP has role in vascular remodeling. Activation of its regulation also alters the morphology of the endothelial plaque and could cause rupture of plaque. MMP also participates in cardiac

remodelling causing myocardiac infarction and progression of dilated cardiomyopathy. [56]

MMP maintains structural integrity of the heart and blood vessels. It also maintains framework for cell anchoring, function, phenotype, and communication. MMP is responsible to promote cell survival or apoptosis, growth factor and cause diastolic stiffness. Another function of MMPs is as a potent protein-degradating and modifying enzymes.[56]

MMP is regulated by the pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α). Extracellular MMP inducers are regulating the production of proenzymes by smooth muscle cells, fibroblast or myocytes. MMP inducers also responsible for transporting them to extracellular matrix. Inhibition of MMP, plasminogen activators or cytokines may reduce the risk of cardiac rupture that lead to myocardial infaction as a result of matrix disruption of MMP [56-57]. Meanwhile, there is a natural inhibitor of MMP, which is tissue inhibitors of metalloproteinases (TIMP). TIMP functions in neutralizing MMP activity.

In association of MMP, TIMP and DCM, recent studies showed that diminished MMP-2 activity is related to cardiac fibrosis in the study of experimental DCM. By observing the STZ-diabetic condition in mice, there is association between cardiac fibrosis and dysregulated degradation of extracellular matrix. It is caused by diminished MMP-2 activity. In addition, there are increased Smad7 and TIMP-2 and decreased MT1-MMP protein expression, which lead to dilated and ischemic heart disease [58]. Li et al. also observed low level of MMP-2 expression and elevated TIMP-2 gene expression in myocardium diabetic rats. This study showed that it may lead to collagen degradation impairment and contribute to the matrix deposition in DCM. Serum TIMP-2 level could act as a marker for early diagnosis of DCM. [59]

MMP-7 also related to diastolic dysfunction and complications of microvascular. Patient with diastolic dysfunction shows an elevation in MMP-9 and reduction in TIMP-1/MMP-9 [60]. There is another investigation demonstrated that serum MMP can be a quantitative biomarkers for myocardial fibrosis. Fibrosis and cardiac event in female with cardiac hypertrophic cadiomyopathy can also be detected using MMP-9 [61]. It is also potential biomarker for cardiac remodeling, both in animal models and clinical studies. In animal experiments, MMP-9 expression significantlyelevated and is associated with inflammation, extracellular matrix degradation and synthesis, diabetic microvascular complications, and also cardiac dysfunction. MMP-9 correlates with the acute-phase reactant proteins IL-6, hs-CRP, and fibrinogen. This correlation indicates that MMP-9 could have its own pathophysiological significance in cardiovascular mortality. The elevation of MMP-9 suggests elevation of myocardial collagen degradation [7]. This reveals that both MMP and TIMP may detect structural and functional heart alternation in diabetic patients.

1.6 MicroRNA (miRNA)

MicroRNA (miRNA) is a single-stranded molecule, consists of 22 non-coding nucleotides. It modulates gene expression and increase mRNA activation [62–64]. MicroRNA affects gene expression by general mechanism such as DNA methylation, and histone modification. [65]

miRNA is important to regulate genes related to hypertrophy of cardiomyocytes, oxidative stress, apoptosis, cardiac fibrosis, and fetal gene program that contribute to DCM. Previous studies showed that cardiac miRNAs contributes to regulation of both transcriptional and post-transcriptional in heart

failure and DCM. Cardiac remodeling and the development of heart failure are associated with the alteration of synthesis and levels of specific mRNA. [66–68]. The miRNAs also has roles in the progression of cardiac hypertrophy, heart failure, and tissue remodeling by targetting the mitochondrial function, apoptosis, fibrosis, pyroptosis, neurohormone secretion, ROS production, Ca^{2+} perturbation, and reactivation of a fetal gene program [62,69]. In addition, under hyperglycemic condition, miRNA-mediated signals can be transferred to other cells or tissues. [63-70]

The regulation of miRNA signaling pathways leads to cardiac hypertrophy, including IGF-1, TGF-β, thyroid hormone, and calcineurin cascade in response to stresses [71]. One of miRNA family, marked as miR-133 is expressed specifically in cardiac and skeletal muscle. Feng et al. reported that the derivated expression of miR-133a causing hypertrophic progression in diabetic mice. MiR-133a is also a target of myocyte enhancer factor-2C (MEF-2C), that leads fibrosis and myocardial hypertrophy. Moreover, miR-133a is also associated with fibrosis through TGF-β1 pathway.[72-73]

Mitochondrial damage, inflammation, activated RAAS, and increased of oxidative stress are major molecular and cellular mechanism of DCM and cardiac dysfunction. Oxydative stress is associated with dysregulation of certain miRNA, such as miR-1, miR-144, miR-133, miR-125b, miR155, miR-210, miR-373, and miR-221 [74]. Recent studies investigated that miRNA-144 inhibition abates oxidative stress and diminish apoptosis in STZ-induced diabetic mice hearts [75]. The downregulation of miR-373 also associated with oxidative stress induced by hyperglicemia. This leads to diabetic cardiomyopathy. [76]

MiRNA modulates various pathways in the pathogenesis of DCM. In addition, circulating miRNAs in blood are stable and it could be a potential biomarkers for DCM. The alteration of circulating miRNA in each phase of DCM shows that it may be used to assess the progression of disease and allow the clinicians to give early intervention [77]. Recent studies showed that miR-9 is a potential serum biomarker in DCM. Its anti-pyroptosis effect on human ventricular cardiomyocytes may targets ELAVL1 gene. Jeyabal et al. also investigate that miR-9 inhibits hyperglicemia-induced pyropsitosis in cardiomyocytes. It results in DCM patient the downregulation of miR-9. [76,78]

Another animal experiment in rats model results in the upregulation of miR-29 associated with cardiac structural damage in Zucker diabetic fatty (ZDF) heart that targets MCL-1 [79]. These conclude that alterated miRNA profile in myocardium and circulation explained the underlying pathology of diabetic cardiomyopaty, potentially can be used as active biomarkers.

1.7 Transforming growth factor-β (TGF-β)

Transforming growth factor-β (TGF-β) is a multifunctional cytokine produced by various types of cells and affect the cell cycle. It is encoded by 33 genes in mammals [80-81]. TGF-β divided into three members including TGF-β1, TGF-β2, and TGF-β3 which expression of every isoform is temporally and spatially distinct. TGF-β has key role in regulating cell growth and differentiation. TGF-β are also expressed in fibrotic tissues, particularly TGF-β1. [80–82]

The activation and differentiation of fibroblasts are stimulated by *TGF-β* activity. Myofibroblast consists of gap junction formation and a contractile apparatus. It elevates proliferation and migration of fibroblast, also induces recruitment of inflammatory

cells, ECM deposition, and collagen synthesis [80,83]. In addition, TGF-β stimulates matrix preservation and deposition by increasing synthesis of matrix protein and shifting the balance between matrix-degrading and matrix-preserving signals. TGF-β maintains matrix preserving signaling by inhibiting MMP and inducing TIMP and PAI-1. In conclusion, TGF-β induces extracellular matrix deposition. [83-84]

Recent studies showed that TGF-β responsiveness significantly increases mobilization of TGF-β receptors in patients with high glucose level. Altered expression of microRNA may responsible in TGF-β activation in diabetic heart. For example, overexpression MicroRNA-98 inhibits expression of TGF-β-receptor-I (TGF-βRI), which could inhibits differentiation and collagen accumulation by TGF-β1. Leptin in diabetes may also induce activation of TGF-β signaling and stimulate TGF-βRII [84-85].
Diabetes mellitus contributes in generating ROS production through its molecular interaction with TGF-β. ROS regulates cell survival and cell apoptosis. Evidence showed that ROS regulate TGF-β signaling pathway through Smad2 activity. TGF-β also generates redox imbalance by elevating ROS production and suppressing antioxidant enzymes. It also increases mitochondrial ROS production in various cells [81]. Chronic accumulation of ROS causes oxidative stress, inflammation, and several alteration such as cardiomyocytes death in diabetic patients. [81,86]

TGF-β has been investigated that it may induce fibrosis in development of diabetic heart disease. Prior study compares three group of subject including control group, DM patients group, and DM patients with diastolic dysfunction group. The results show that DM patients with resulted in increased TGF-β level. Compared to diabetes mellitus group alone, TGF-β levels are found significantly higher in diabetes mellitus with diastolic dysfunction patients [49]. Therefore, TGF-β can be a promising cardiac biomarker for DCM because it appears in early stage diabetic heart alteration. TGF-β also may predict future prognosis and severity of the disease. Moreover TGF-β detection is a less invasive procedure than current available examination tool.

Conclusion

Achieving early diagnosis of asymptomatic DCM is important to prevent the progression of irreversible morphological alteration, such as fibrosis, that leads to contractility impairment. Current diagnostic approach including MRI, echocardiography, NT-proBNP, and nuclear imaging might detect DCM. This examination has limitation in more complex, harmful, less specific, and not cost-effective. They tend to give result in late phase of DCM.

There are novel biomarkers to identify early sign of cardiac functional change. Gal-3 might represent valuable implement, together with FGF-21, H-FABP, IGFBP, MMP and TIMP, miRNA, and TGF-β levels in order to detect climacteric of the metabolic and functional cardiac status. Increased plasma levels of Gal-3, profibrotic actors, correlated with insulin resistance, fibrogenesis, and extracellular remodeling. FGF-21, as metabolic actors, roles in states like insulin resistance, lipid accumulation, and gluconeogenesis. H-FABP discloses low-level myocardial injury in prediabetic state. Overexpression of IGFBP-7 correlated with insulin resistance. MMP and TIMP play roles in cardiac remodeling. TGF-β has been investigated that it may induce fibrosis. MiRNA modulates various pathways in pathogenesis of DCM. The alteration of these biomarkers in each phase of DCM show that it can be used to assess the progression of disease and allow the clinicians to give early intervention which alleviate its mortality rate.

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References

1. Lee W-S and Kim J. 2017. Diabetic cardiomyopathy: where we are and where we are going. Korean J. Intern. Med. 32 404–21.
2. Zhang P-Y. 2014. Cardiovascular disease in diabetes. Eur. Rev. Med. Pharmacol. Sci. 18 2205–14.
3. Leon B M and Maddox T M. 2015. Diabetes and cardiovascular disease : Epidemiology, biological mechanisms, treatment recommendations and future research. 6 1246–58.
4. Jia G, Hill MA and Sowers JR. 2018. Diabetic cardiomyopathy: An update of mechanisms contributing to this clinical entity Circ. Res. 122 624–38.
5. Alonso N, Moliner P and Mauricio D. 2018. Pathogenesis, Clinical Features and Treatment of Diabetic Cardiomyopathy. Adv. Exp. Med. Biol. 1067 197–217.
6. Gilca G, Stefanescu G, Badulescu O, Tanase D, Bararu I and Ciocoiu M. 2017. Diabetic Cardiomyopathy : Current Approach and Potential Diagnostic and Therapeutic Targets 2017.
7. Palomer X, Pizarro-Delgado J and Vázquez-Carrera M. 2018. Emerging Actors in Diabetic Cardiomyopathy: Heartbreaker Biomarkers or Therapeutic Targets? Trends Pharmacol. Sci. 39.
8. Jia G, DeMarco V G and Sowers J R. 2016. Insulin resistance and hyperinsulinemia in diabetic cardiomyopathy Nat. Rev. Endocrinol. 12 144.
9. Wang Z V and Hill J A. 2015. Diabetic cardiomyopathy: catabolism driving metabolism. Circulation 131 771–3.
10. Borghetti G, von Lewinski D, Eaton D M, Sourij H, Houser S R and Wallner M. 2018. Diabetic Cardiomyopathy: Current and Future Therapies. Beyond Glycemic Control. Front. Physiol. 9 1514.
11. Rijzewijk L J, van der Meer R W, Smit J W A, Diamant M, Bax J J, Hammer S., et al. 2008. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J. Am. Coll. Cardiol. 52 1793–9.
12. Lorenzo O, Picatoste B, Ares-Carrasco S, Ramirez E, Egido J and Tunon J. 2011. Potential role of nuclear factor kappaB in diabetic cardiomyopathy. Mediators Inflamm. 2011 652097.
13. Palomer X, Salvado L, Barroso E and Vazquez-Carrera M. 2013. An overview of the crosstalk between inflammatory processes and metabolic dysregulation during diabetic cardiomyopathy. Int. J. Cardiol. 168 3160–72.
14. Asghar O, Al-Sunni A, Khavandi K, Khavandi A, Withers S, Greenstein A., et al. 2009. Diabetic cardiomyopathy. Clin. Sci. (Lond). 116 741–6.
15. Richter K and Kietzmann T. 2016. Reactive oxygen species and fibrosis: further evidence of a significant liaison Cell Tissue Res. 365 591–605.
16. Díaz-Alvarez L and Ortega E. 2017. The Many Roles of Galectin-3, a Multifaceted Molecule, in Innate Immune Responses against Pathogens Mediators Inflamm. 2017 1–10.
17. Johannes L, Jacob R and Leffler H. 2018. Galectins at a glance J. Cell Sci. 131 jcs208884.
18. Argüeso P and Panjwani N. 2011. Focus on Molecules: Galectin-3 Exp. Eye Res. 92 2–3.

19. Brinchmann M F, Patel D M and Iversen M H. 2018. The Role of Galectins as Modulators of Metabolism and Inflammation Mediators Inflamm. 2018 1–11.
20. Li P, Liu S, Lu M, Bandyopadhyay G, Oh D, Imamura T., et al. 2016. Hematopoietic-Derived Galectin-3 Causes Cellular and Systemic Insulin Resistance Cell 167 973–984.e12.
21. Berezin A E. 2017. Cardiac biomarkers in diabetes mellitus: New dawn for risk stratification? Diabetes Metab. Syndr. Clin. Res. Rev. 11 S201–8.
22. De Boer R A and Van Der Velde A R. 2013. Galectin-3: A new biomarker for heart failure progression and prognosis LaboratoriumsMedizin 37 251–60.
23. Zhong X, Qian X, Chen G and Song X. 2018. The role of galectin-3 in heart failure and cardiovascular disease Clin. Exp. Pharmacol. Physiol. 197–203.
24. Gruson D, Ahn S, Rousseau M and Hermans M. 2014. Serum Galectin-3 Is Elevated and Related to Cardiac Biomarkers in Types 2 Diabetes J. Card. Fail. 20 S43.
25. Yin Q S, Shi B, Dong L and Bi L. 2014. Comparative study of galectin-3 and B-type natriuretic peptide as biomarkers for the diagnosis of heart failure J. Geriatr. Cardiol. 11 79–82.
26. Staiger H, Keuper M, Berti L, de Angelis M H and Häring H U. 2017. Fibroblast growth factor 21-metabolic role in mice and men Endocr. Rev. 38 468–88.
27. Planavila A, Redondo-Angulo I and Villarroya F. 2015. FGF21 and Cardiac Physiopathology Front. Endocrinol. (Lausanne). 6 1–7.
28. Itoh N, Ohta H and Konishi M. 2015. Endocrine FGFs: Evolution, Physiology, Pathophysiology, and Pharmacotherapy Front. Endocrinol. (Lausanne). 6 1–9.
29. Aubert G, Vega R B and Kelly D P. 2013. Perturbations in the gene regulatory pathways controlling mitochondrial energy production in the failing heart Biochim. Biophys. Acta - Mol. Cell Res. 1833 840–7.
30. Chen C, Meng Z, Zheng Y, Hu B and Shen E. 2018. Fibroblast growth factor 21 inhibition aggravates cardiac dysfunction in diabetic cardiomyopathy by improving lipid accumulation Exp. Ther. Med. 15 75–84.
31. Tanajak P, Sa-Nguanmoo P, Wang X, Liang G, Li X, Jiang C., et al. 2016. Fibroblast growth factor 21 (FGF21) therapy attenuates left ventricular dysfunction and metabolic disturbance by improving FGF21 sensitivity, cardiac mitochondrial redox homeostasis and structural changes in pre-diabetic rats Acta Physiol. 217 287–99.
32. Tanajak P, Pongkan W, Chattipakorn S C and Chattipakorn N. 2018. Increased plasma FGF21 level as an early biomarker for insulin resistance and metabolic disturbance in obese insulin-resistant rats Diabetes Vasc. Dis. Res. 15 263–9.
33. Muralidaran Y and Viswanathan P. 2015. Diabetic Cardiomyopathy : A New Perspective of Mechanistic Approach Diabetic Cardiomyopathy : A New Perspective of Mechanistic Approach.
34. Luo Y and Lu W. 2018. Serum Levels of FGF21 and Prediction of Cardiovascular Events Cardiol. 139 219–21.
35. Yang H, Feng A, Lin S, Yu L, Lin X, Yan X., et al. 2018. Fibroblast growth factor-21 prevents diabetic cardiomyopathy via AMPK-mediated antioxidation and lipid-lowering effects in the heart article /13/2 /13/95 /64/60 /96/95 Cell Death Dis. 9.

36. Zhang C, Huang Z, Gu J, Yan X, Lu X, Zhou S., et al. 2015. Fibroblast growth factor 21 protects the heart from apoptosis in a diabetic mouse model via extracellular signal-regulated kinase 1/2-dependent signaling pathway Diabetologia 58 1937–48.
37. Wu F, Wang B, Zhang S, Shi L, Wang Y, Xiong R., et al. 2017. FGF21 ameliorates diabetic cardiomyopathy by activating the AMPK-paraoxonase 1 signaling axis in mice Clin. Sci. 131 1877–93.
38. Ong K L, Januszewski A S, O'Connell R, Jenkins A J, Xu A, Sullivan D R., et al. 2015. The relationship of fibroblast growth factor 21 with cardiovascular outcome events in the Fenofibrate Intervention and Event Lowering in Diabetes study Diabetologia 58 464–73.
39. Elhini S, Matta R, Saad M, Mostafa H and AbedelfadeeL A. 2017. Fibroblast growth factor-21 is a novel linkage between metabolic parameters, cardiovascular risk, and nephropathy in prediabetes Egypt. J. Obesity, Diabetes Endocrinol. 3 22–31.
40. Beysel S, Kizilgul M, Ozbek M, Caliskan M, Kan S, Apaydin M., et al. 2017. Heart-type fatty acid binding protein levels in elderly diabetics without known cardiovascular disease Clin. Interv. Aging 12 2063.
41. Schoenenberger A W, Stallone F, Walz B, Bergner M, Twerenbold R, Reichlin T., et al. 2016. Incremental value of heart-type fatty acid-binding protein in suspected acute myocardial infarction early after symptom onset Eur. Hear. J. Acute Cardiovasc. Care 5 185–92.
42. Viswanathan K, Kilcullen N, Morrell C, Thistlethwaite S J, Sivananthan M U, Hassan T B., et al. 2010. Heart-type fatty acid-binding protein predicts long-term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome who are troponin-negative J. Am. Coll. Cardiol. 55 2590–8.
43. Haltern G, Peiniger S, Bufe A, Reiss G, Gülker H and Scheffold T. 2010. Comparison of usefulness of heart-type fatty acid binding protein versus cardiac troponin T for diagnosis of acute myocardial infarction Am. J. Cardiol. 105 1–9.
44. Karbek B, Özbek M, Bozkurt N C, Ginis Z, Güngünes A, Ünsal İ Ö., et al. 2011. Heart-Type Fatty Acid Binding Protein (H-FABP): Relationship with arterial ıntima-media thickness and role as diagnostic marker for atherosclerosis in patients with ımpaired glucose metabolism Cardiovasc. Diabetol. 10 37.
45. Shearer J, Fueger P T, Wang Z, Bracy D P, Wasserman D H and Rottman J N. 2008. Metabolic implications of reduced heart-type fatty acid binding protein in insulin resistant cardiac muscle Biochim. Biophys. Acta (BBA)-Molecular Basis Dis. 1782 586–92.
46. Akbal E, Özbek M, Güneş F, Akyürek Ö, Üreten K and Delibaşı T. 2009. Serum heart type fatty acid binding protein levels in metabolic syndrome Endocrine 36 433–7.
47. Komamura K, Sasaki T, Hanatani A, Kim J, Hashimura K, Ishida Y., et al. 2006. Heart-type fatty acid binding protein is a novel prognostic marker in patients with non-ischaemic dilated cardiomyopathy Heart 92 615–8.
48. Goto T, Takase H, Toriyama T, Sugiura T, Sato K, Ueda R., et al. 2003. Circulating concentrations of cardiac proteins indicate the severity of congestive heart failure Heart 89 1303–7.
49. Shaver A, Nichols A, Thompson E, Mallick A, Payne K, Jones C., et al. 2016. Role of serum biomarkers in early detection of diabetic cardiomyopathy in the West Virginian population Int. J. Med. Sci. 13 161.

50. Liu Y, Wu M, Ling J, Cai L, Zhang D, Gu H F., et al. 2015. Serum IGFBP7 levels associate with insulin resistance and the risk of metabolic syndrome in a Chinese population Sci. Rep. 5 10227.
51. Fakhruddin S, Alanazi W and Jackson K E. 2017. Diabetes-induced reactive oxygen species: mechanism of their generation and role in renal injury J. Diabetes Res. 2017.
52. Lorenzo-Almoros A, Tunon J, Orejas M, Cortés M, Egido J and Lorenzo Ó. 2017. Diagnostic approaches for diabetic cardiomyopathy Cardiovasc. Diabetol. 16 28.
53. Guo X H, Liu L X, Zhang H Y, Zhang Q Q, Li Y, Tian X X., 2014. Insulin-like growth factor binding protein-related protein 1 contributes to hepatic fibrogenesis J. Dig. Dis. 15 202–10.
54. Gandhi P U, Gaggin H K, Sheftel A D, Belcher A M, Weiner R B, Baggish A L., et al. 2014. Prognostic usefulness of insulin-like growth factor-binding protein 7 in heart failure with reduced ejection fraction: a novel biomarker of myocardial diastolic function? Am. J. Cardiol. 114 1543–9.
55. Januzzi Jr J L, Packer M, Claggett B, Liu J, Shah A M, Zile M R., et al. 2018. IGFBP7 (Insulin-Like Growth Factor–Binding Protein-7) and Neprilysin Inhibition in Patients With Heart Failure Circ. Hear. Fail. 11 e005133.
56. Liu P, Sun M and Sader S. 2006. Matrix metalloproteinases in cardiovascular disease Can. J. Cardiol. 22 25B–30B.
57. Sun M, Dawood F, Wen W-H, Chen M, Dixon I, Kirshenbaum L A., et al. 2004. Excessive tumor necrosis factor activation after infarction contributes to susceptibility of myocardial rupture and left ventricular dysfunction Circulation 110 3221–8.
58. Van Linthout S, Seeland U, Riad A, Eckhardt O, Hohl M, Dhayat N., et al. 2008. Reduced MMP-2 activity contributes to cardiac fibrosis in experimental diabetic cardiomyopathy Basic Res. Cardiol. 103 319–27.
59. Li Q, Sun S, Wang Y, Tian Y and Liu M. 2007. The roles of MMP-2/TIMP-2 in extracellular matrix remodeling in the hearts of STZ-induced diabetic rats Acta Cardiol. 62 485–91.
60. Ban C R, Twigg S M, Franjic B, Brooks B A, Celermajer D, Yue D K., et al. 2010. Serum MMP-7 is increased in diabetic renal disease and diabetic diastolic dysfunction Diabetes Res. Clin. Pract. 87 335–41.
61. Münch J, Avanesov M, Bannas P, Säring D, Krämer E, Mearini G., et al. 2016. Serum matrix metalloproteinases as quantitative biomarkers for myocardial fibrosis and sudden cardiac death risk stratification in patients with hypertrophic cardiomyopathy J. Card. Fail. 22 845–50.
62. Condorelli G, Latronico M V G and Dorn G W 2nd. 2010. microRNAs in heart disease: putative novel therapeutic targets? Eur. Heart J. 31 649–58.
63. Condorelli G, Latronico M V G and Cavarretta E. 2014. microRNAs in cardiovascular diseases: current knowledge and the road ahead. J. Am. Coll. Cardiol. 63 2177–8.
64. Saraiya A A, Li W and Wang C C. 2013. Transition of a microRNA from repressing to activating translation depending on the extent of base pairing with the target. PLoS One 8 e55672.
65. Voelter-Mahlknecht S. 2016. Epigenetic associations in relation to cardiovascular prevention and therapeutics Clin. Epigenetics 8 4.

66. Zhou Q, Lv D, Chen P, Xu T, Fu S, Li J., et al. 2014. MicroRNAs in diabetic cardiomyopathy and clinical perspectives. Front. Genet. 5 185.
67. Latronico M V G, Elia L, Condorelli G and Catalucci D. 2008. Heart failure: targeting transcriptional and post-transcriptional control mechanisms of hypertrophy for treatment. Int. J. Biochem. Cell Biol. 40 1643–8.
68. Rao P K, Toyama Y, Chiang H R, Gupta S, Bauer M, Medvid R., et al. 2009. Loss of cardiac microRNA-mediated regulation leads to dilated cardiomyopathy and heart failure. Circ. Res. 105 585–94.
69. Melman Y F, Shah R and Das S. 2014. MicroRNAs in heart failure: is the picture becoming less miRky? Circ. Heart Fail. 7 203–14.
70. Das S, Ferlito M, Kent O A, Fox-Talbot K, Wang R, Liu D., et al. 2012. Nuclear miRNA regulates the mitochondrial genome in the heart. Circ. Res. 110 1596–603.
71. Wang J and Yang X. 2012. The function of miRNA in cardiac hypertrophy. Cell. Mol. Life Sci. 69 3561–70.
72. Feng B, Chen S, George B, Feng Q and Chakrabarti S. 2010. miR133a regulates cardiomyocyte hypertrophy in diabetes. Diabetes. Metab. Res. Rev. 26 40–9.
73. Ruiz M A and Chakrabarti S. 2013. MicroRNAs: the underlying mediators of pathogenetic processes in vascular complications of diabetes. Can. J. diabetes 37 339–44.
74. Jacobs L H, van de Kerkhof J J, Mingels A M, Passos V L, Kleijnen V W, Mazairac A H., et al. 2009. Inflammation, overhydration and cardiac biomarkers in haemodialysis patients: a longitudinal study Nephrol. Dial. Transplant. 25 243–8.
75. Li X, Du N, Zhang Q, Li J, Chen X, Liu X., et al. 2014. MicroRNA-30d regulates cardiomyocyte pyroptosis by directly targeting foxo3a in diabetic cardiomyopathy. Cell Death Dis. 5 e1479.
76. Shen E, Diao X, Wang X, Chen R and Hu B. 2011. MicroRNAs involved in the mitogen-activated protein kinase cascades pathway during glucose-induced cardiomyocyte hypertrophy. Am. J. Pathol. 179 639–50.
77. Tijsen A J, Pinto Y M and Creemers E E. 2012. Circulating microRNAs as diagnostic biomarkers for cardiovascular diseases. Am. J. Physiol. Heart Circ. Physiol. 303 H1085-95.
78. Jeyabal P, Thandavarayan R A, Joladarashi D, Suresh Babu S, Krishnamurthy S, Bhimaraj A., et al. 2016. MicroRNA-9 inhibits hyperglycemia-induced pyroptosis in human ventricular cardiomyocytes by targeting ELAVL1. Biochem. Biophys. Res. Commun. 471 423–9.
79. Arnold N, Koppula P R, Gul R, Luck C and Pulakat L. 2014. Regulation of cardiac expression of the diabetic marker microRNA miR-29. PLoS One 9 e103284.
80. Yue Y, Meng K, Pu Y and Zhang X. 2017. Transforming growth factor beta (TGF-beta) mediates cardiac fibrosis and induces diabetic cardiomyopathy. Diabetes Res. Clin. Pract. 133 124–30.
81. Liu R-M and Desai L P. 2015. Reciprocal regulation of TGF-beta and reactive oxygen species: A perverse cycle for fibrosis. Redox Biol. 6 565–77.
82. Biernacka A, Dobaczewski M and Frangogiannis N G. 2011. TGF-beta signaling in fibrosis. Growth Factors 29 196–202.

83. Morikawa M, Derynck R and Miyazono K. 2016. TGF-beta and the TGF-beta Family: Context-Dependent Roles in Cell and Tissue Physiology. Cold Spring Harb. Perspect. Biol. 8.
84. Cheng R, Dang R, Zhou Y, Ding M and Hua H. 2017. MicroRNA-98 inhibits TGF-beta1-induced differentiation and collagen production of cardiac fibroblasts by targeting TGFBR1. Hum. Cell 30 192–200.
85. Budi E H, Muthusamy B-P and Derynck R. 2015. The insulin response integrates increased TGF-beta signaling through Akt-induced enhancement of cell surface delivery of TGF-beta receptors. Sci. Signal. 8 ra96.
86. Redza-Dutordoir M and Averill-Bates D A. 2016. Activation of apoptosis signaling pathways by reactive oxygen species. Biochim. Biophys. Acta 1863 2977–92.