Progress in Cardiovascular Diseases 62 (2019) 315–326

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Diabetic cardiomyopathy - A comprehensive updated review

Ghulam Murtaza [a], Hafeez Ul Hassan Virk [b], Muhammad Khalid [a], Carl J. Lavie [c], Hector Ventura [c], Debabrata Mukherjee [d], Vijay Ramu [a], Sukhdeep Bhogal [a], Gautam Kumar [e], Madhan Shanmugasundaram [f], Timir K. Paul [a,*]

[a] Department of Internal Medicine, Division of Cardiology, East Tennessee State University, Johnson City, TN, USA
[b] Department of Cardiology, Albert Einstein Healthcare Network, Philadelphia, PA, USA
[c] Department of Cardiology, Ochsner Clinic, New Orleans, LA, USA
[d] Division of Cardiology, Department of Internal Medicine, Texas Tech University, TX, USA
[e] Emory University School of Medicine, Atlanta VA Medical Center, Atlanta, GA, USA
[f] University of Arizona College of Medicine, Tucson, AZ, USA

ARTICLE INFO

Keywords:
Cardiomyopathy
Diabetes
Diastolic dysfunction
Ejection fraction
Heart failure
Risk factors

ABSTRACT

Diabetes causes cardiomyopathy and increases the risk of heart failure independent of hypertension and coronary heart disease. This condition called "Diabetic Cardiomyopathy" (DCM) is becoming a well- known clinical entity. Recently, there has been substantial research exploring its molecular mechanisms, structural and functional changes, and possible development of therapeutic approaches for the prevention and treatment of DCM. This review summarizes the recent advancements to better understand fundamental molecular abnormalities that promote this cardiomyopathy and novel therapies for future research. Additionally, different diagnostic modalities, up to date screening tests to guide clinicians with early diagnosis and available current treatment options has been outlined.

Contents

Abbreviations and acronyms: AGEs, advanced glycation end products; AAs, aldosterone antagonists; ACEI, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor and neprilysin inhibitor; α-SMA, smooth muscle actin; BNP, brain natriuretic peptide; BBs, beta blockers; CVD, cardiovascular disease; CHD, coronary heart disease; CAD, Coronary artery disease; CAN, cardiac autonomic neuropathy; CoQ 10, coenzyme Q10; DCM, diabetic cardiomyopathy; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; EF, ejection fraction; ECM, extracellular matrix; EMB, endomyocardial biopsy; eNOS, endothelial nitric oxide synthase; FFA, free fatty acids; G-SPECT, Gated Single Photon Emission Computed Tomography; GLP-1R, Glucagon-like peptide-1 receptor; HTN, hypertension; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HbA1C, glycated hemoglobin; IBT, incretin-based therapies; LV, left ventricle; LVM, left ventricular mass; LVH, left ventricular hypertrophy; LVEDP, left ventricular end diastolic pressure; LGE, Late-gadolinium enhancement; miRNAs, MicroRNAs; MMP-2, matrix metalloproteinase-2; MRI, magnetic resonance imaging; MAPK, mitogen-activated protein kinase; MCFAs, medium-chain fatty acids; NPADH-oxidase, nicotinamide adenine dinucleotide phosphate oxidase system; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PI3Kg, Phosphoinositide3-kinase gamma; PET, positron emission tomography; RyR, Ryanodine receptors; ROS, reactive oxygen species; RAAS, renin-angiotensin-aldosterone system; RNV, radionuclide ventriculography; RAGE, Receptor for advanced glycation end products; SR, sarcoplasmic reticulum; SGLT-2, sodium-glucose transporter-2; TGL, triglycerides; TGF-β, transforming growth factor–β; TDI, Tissue Doppler Imaging; TZDs, Thiazolidinediones; VHD, valvular heart disease; VLDL, very low density lipoprotein; VEGF, Vascular endothelial growth factor; Vaspin, Visceral adipose tissue–derived serine protease inhibitor.

* Address reprint requests to Timir K. Paul, Division of Cardiology, Department of Internal Medicine, East Tennessee State University, 329 N State of Franklin Rd, Johnson City, TN 37604.
E-mail address: pault@etsu.edu (T.K. Paul).

https://doi.org/10.1016/j.pcad.2019.03.003
0033-0620/

Introduction

There is a well-established relationship between diabetes mellitus (DM) and cardiovascular (CV) disease (CVD). Several studies have demonstrated the epidemiological link between heart failure (HF) and DM. Clearly, DM can increase the risk of HF, even independently of the traditional risk for HF, including hypertension (HTN), coronary heart disease (CHD) and valvular heart disease (VHD). Longstanding DM results in structural and functional changes that lead to development and progression of HF, independent of myocardial ischemic or microvascular atherosclerotic disease process. This disease process was first described in 1972 by Rubler et al on histopathologic evaluation during postmortem examination of DM patients with HF who did not have CHD, HTN or VHD.[1] It was found to be a unique pathological subset that seemed to act independent of the traditional risk factors resulting from direct effects of abnormal myocardial metabolism. This unique form of CVD was termed as diabetic cardiomyopathy (DCM). Later, in the Framingham Heart Study, patient with DM were found to have significantly increased risk of HF independent of the factors that cause accelerated atherogenesis and CHD.[2] Since then many studies have demonstrated the structural and functional changes in the myocardium of patients with DM that are not related to other traditional CVD risk factors.

Structural changes in DCM

There are several structural changes in myocardium of patients with DM that lead to left ventricular (LV) dysfunction. DM causes increased absolute and relative increases in LV wall thickness and LV mass (LVM) independent of obesity, HTN and other factors that could also increase LVM and LV hypertrophy (LVH).[3] Initially there is a subclinical period of these structural and functional abnormalities that result from LVH, fibrosis and impaired myocardial relaxation. Therefore, most of these DM patients with LVH are initially asymptomatic in early phases and gradually become symptomatic with development of clinical HF. Increased LVM reduces diastolic LV filling, thus causing LV diastolic dysfunction that precedes the development of systolic dysfunction. Therefore, historically most of these patients progress from subclinical phase to HF with preserved ejection fraction (EF; HFpEF) and eventually to systolic dysfunction accompanied by HF with reduced ejection fraction (HFrEF). Maisch et al proposed the following classification to define the clinical progression of DCM (Table 1).

Multiple studies have demonstrated the independent association of DM and increased LVM[5,6]; LVH leads to reduction in the left ventricular compliance impairing the diastolic filling, prolongation of isovolumetric relaxation, increased atrial filling and LV end diastolic pressure (LVEDP), leading to LV dysfunction.[7] Most of these patients at this stage I DCM are asymptomatic. The prevalence of diastolic dysfunction in DM patients has been estimated to be approximately 52–60% based on recent studies using rigorous Doppler methods that could detect early and mild diastolic dysfunction.[8] In these patients with early stage DCM, though myocardial dysfunction is subclinical, stress situations such as exercise can reveal impaired exercise-induced augmentation in systolic performance implying impaired contractile reserve. This subtle systolic dysfunction could be present in association with diastolic dysfunction which precedes the development of systolic dysfunction with reduced LVEF (Fig. 1).

Table 1
Proposed classification of DCM.[4]

Stages of diabetic cardiomyopathy	Clinical phenotype
Stage I	Diastolic dysfunction with normal EF[a]
Stage II	Combined systolic and diastolic dysfunction
Stage III	Systolic and diastolic dysfunction with microvascular disease/coronary atherosclerosis without obstructive CHD
Stage IV	Clinical overt ischemia/infarct causing HF

EF: ejection fraction; DCM: diabetic cardiomyopathy; HF: heart failure.
[a] Excluded coronary heart disease (CHD), valvular disease and uncontrolled hypertension.

Pathophysiology of DCM

The pathophysiology of DCM is multifactorial and involves complex metabolic pathways involving alteration in fatty acid metabolism, chronic hyperglycemia- induced changes in circulating hormones and cytokines. These pathways have been summarized in Table 3. The molecular abnormalities induced by the DM milieu are different from those elicited by HTN or ischemia.

Deranged calcium homeostasis

In DCM, contractility of myocytes is affected by impaired insulin signaling that reduces glucose uptake into cardiac myocytes and decreased activity of efflux pumps increasing intracellular calcium,[9] thus affecting the dynamic of the contraction-relaxation cycle of the working myocytes.

During normal excitation-contraction coupling, there is cyclic rise and fall in intracellular calcium that leads to periodic contraction and relaxation of working myocytes. During phase 3 of normal action potential of cardiac cell membranes, voltage gated L- type calcium channels open, allowing influx of calcium that triggers further release of stored calcium in cardiac myocytes from the sarcoplasmic reticulum (SR). Release of calcium from the SR is mediated by Ryanodine receptors (RyR). This excess calcium leads to engagement of actin and myosin filaments. After contraction is achieved, calcium exchange channels and pumps become active and restore calcium back into SR.[10]

In patients with DM, oxidative damage is induced by production of reactive oxygen species (ROS) as a result of abnormal insulin metabolic signaling. High susceptibility of RyR to this oxidative stress impairs the function of these channels.[11] By the same token, these oxyradicals generated as a consequence of insulin deficiency in animal models have been shown to induce significant depression of ATPase pumps and exchange channels.[12] Abnormal insulin metabolic signaling decreases insulin-stimulated coronary endothelial nitric oxide (NO) synthase (eNOS) activity and NO production increasing cardiomyocyte intracellular Ca^{2+}/Ca^{2+} sensitization and reducing sarcoplasmic Ca^{2+} uptake.[13] These defects contribute to development of intracellular calcium overload with resulting manifestation of increased cardiac stiffness and impaired relaxation which are core features of DCM (Fig. 2).

Mitochondrial fatty acid oxidation alterations

Alterations in beta-oxidation of fatty acids occur during ischemia. The same change has been demonstrated in DCM that contributes to cardiac pathology. Metabolic remodeling in DCM involves loss of ability of myocardial cells to adjust its relative metabolism of carbohydrates and fatty acids. The loss of this metabolic flexibility means that the heart relies almost exclusively on mitochondrial fatty acid β-oxidation. In the setting of DM, the occurrence of insulin resistance in the myocardium, together with increased rates of systemic lipolysis and changes in hormonal milieu of DM heart contributes to increased fatty acid oxidation.[14] This increase in mitochondrial metabolism of fatty acid in relation to carbohydrate oxidation has the potential to decrease cardiac efficiency and contributes to the observed impaired heart function seen in DCM. In a study conducted by Herrero et al, 11 patients with type 1 DM were compared with 11 healthy non-DM patients where mitochondrial fatty acid oxidation and utilization percentage was found to be significantly higher in the DM cohort.[15] Similar results have been demonstrated in animal models of DM with insulin resistance.[16] This preferential utilization of fatty acid oxidized by the mitochondria in relation to carbohydrate oxidation is contributed by multiple mechanisms which are shown in Table 2.

Myocardial fibrosis: role of transforming growth factor–β (TGF-β)

Myocardial fibrosis plays a key role in development of several of the pathological changes that are associated with DCM, including LVH, diastolic dysfunction and systolic dysfunction.[17] The accentuation of fibrotic changes in DM patients with HF has been elucidated on both of the histopathological analysis of autopsy specimens and quantification of fibrosis using newly developed cardiac diffusion weighted imaging and T1 mapping techniques.[18]

The development of DM-induced cardiac fibrosis involves complex signaling pathways that leads to remodeling of extracellular matrix (ECM). Abnormal gene expression, signal transduction and activation of secondary messenger pathways trigger imbalance between ECM synthesis and breakdown. Work of Li et al reveals that increased activity of smooth muscle actin (α-SMA), transforming growth factor–β (TGF-β) and reduced functioning of active matrix metalloproteinase-2 (MMP-2) play a vital role in development of cardiac fibrosis.[19] Increased activity of TGF-β is postulated to be the result of hyperglycemia which increases the transcription of the genes that encode TGF-β resulting in elevated levels of this fibrogenic agent.[20] The exact mechanism by which hyperglycemia leads to activation of TGF-β is unknown. Nonetheless, TGF-β activation leads to cardiac fibrosis through the activation of SMAD-dependent pathway which are a family of structurally related proteins that activate the intracellular signaling cascade promoting signaling pathways that play crucial roles in the development of myocardial fibrosis(Fig. 4).[21,22]

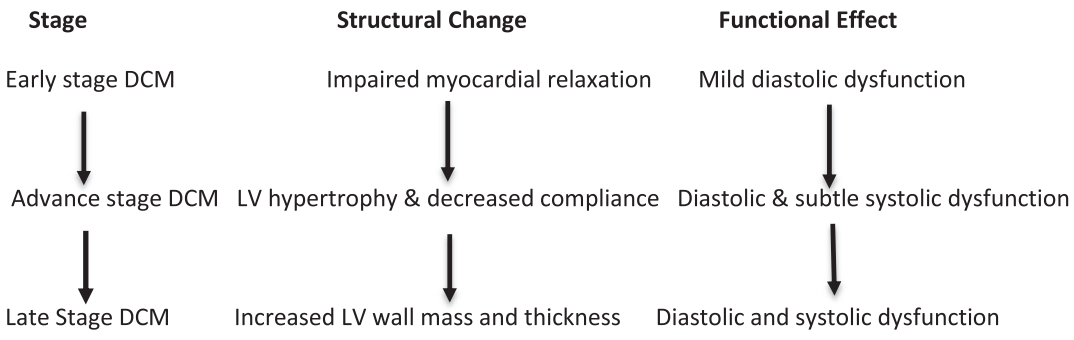

Fig. 1. Flow chart showing clinical progression of DCM. DCM: Diabetic cardiomyopathy; LV: left ventricle.

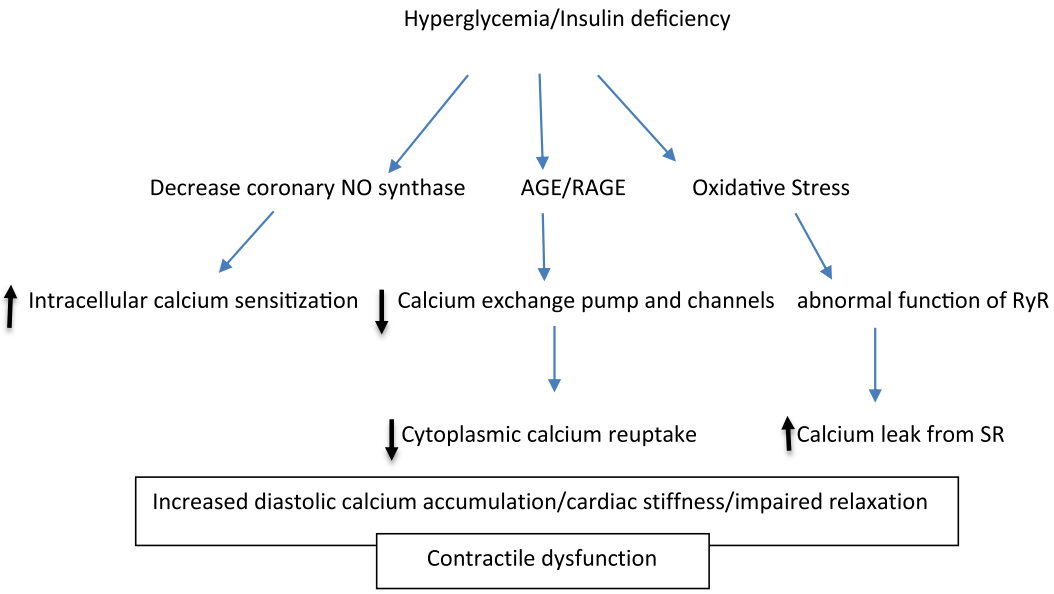

Fig. 2. Flow chart illustrating different mechanisms involved in deranged calcium homeostasis in cardiac myocytes. AGEs: Advanced glycation end products, NO: nitric oxide, RyR: Ryanodine receptor, RAGE: Receptor for advanced glycation end products, SR: sarcoplasmic reticulum.

Role of advanced glycation end products (AGE)

Advanced glycation is a major pathway in development of various DM complications, with DCM being one of them. Chronic hyperglycemia induces glycation of fibrinogen and albumin resulting in generation of advanced AGE and upregulates the development of receptors for these AGEs. Interaction with these receptors begins the series of events that lead to oxidative stress and elaborates inflammatory cytokines causing increased inflammation promoting vascular and myocardial damage. Some of these abnormal signaling pathways are mediated through Janus kinase and mitogen-activated protein kinase (MAPK) pathway activation.[23] Increased serum levels of these products positively correlated with isovolumetric relaxation time and LV diameter during diastole signifying myocardial stiffness.[24] Formation of AGE in myocardial cells causes cross-linking of collagen molecules to each other.[25] This leads to the loss of collagen elasticity with subsequent reduction of myocardial compliance. In addition to this cross linking, they also increase production of reactive oxygen species (ROS) and promote myocardial fibrosis.

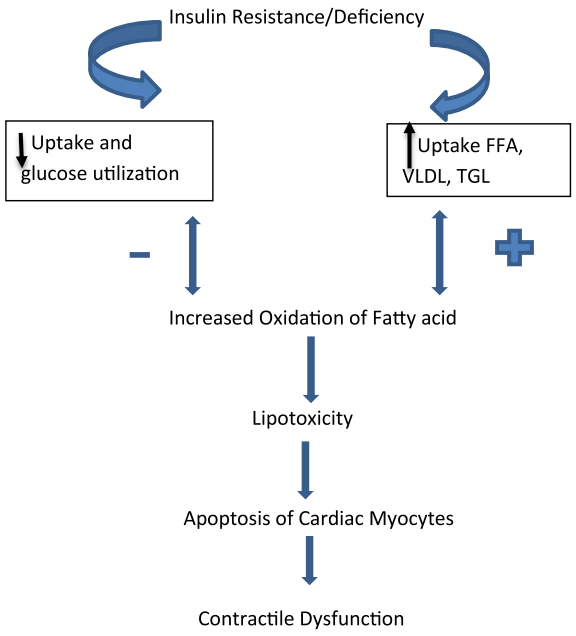

Fig. 3. Mechanisms of cardiac lipotoxicity. FFA: Free fatty acids, TGL: triglyceride, VLDL: very low-density lipoprotein.

Reactive oxygen species

Hyperglycemia can alter several signaling pathways in myocardial cells some of which are discussed above including the formation of AGEs, as well as the secretion of the pro-inflammatory cytokines. Most recent studies show that there are certain signaling pathways that are directly triggered by hyperglycemia and appear to have a pivotal role in the production of ROS which involve diacylglycerol, the activation of protein kinase C and nicotinamide adenine dinucleotide phosphate oxidase system (NPADH-oxidase).[26] Increased cardiomyocyte NAPDH activity is associated with increased production of free radicals which cause oxidative myocardial injury.[27]

Inflammation

Inflammation is a key pathogenic feature of cardiomyopathy in DM patients and DCM. Hyperglycemia and increased metabolism of free fatty acids is associated with upregulation of pro-inflammatory cytokines such as Interleukin-6, tumor necrosis factor-α, Monocyte chemoattractant protein 1 and nuclear factor-κB (NF-Kb). The NF-κB p65 gets activated in cardiac myocytes of DM patients.[28] NF-κB

Table 2
Different mechanisms involved in promoting fatty acid utilization in cardiac myocytes.

1. Increased circulating levels of free fatty acids and triglycerides
2. Increased uptake of free fatty acids due to increased translocation of fatty acids transported into mitochondrial membrane
3. Overexpression of peroxisome proliferator-activated receptors (PPAR alpha, -beta/delta and -gamma) genes, members of the nuclear receptor transcription factor superfamily which enhance the fatty acid oxidation rates
4. Feedback inhibition of metabolic pathways oxidizing glucose caused by accelerated oxidation of fatty acids
5. Increase in intramyocardial triglyceride stores

The end products of these mechanisms are deranged metabolites that cause lipotoxicity (Fig. 3). These toxic metabolites lead to apoptosis of cardiac myocytes which results in contractile dysfunction contributing to cardiomyopathy.[14]

Table 3
Summary of different metabolic processes involved in the pathophysiology of DCM.

Pathological mechanisms	Pathophysiological pathway	Structural change	Functional alteration
Deranged Ca++ homeostasis	Calcium leak from RyR Reduced sarcolemmal elimination of Ca++ Prolonged Ca++ transients	Mitochondrial leakage of toxic proteins, myocardial cytotoxicity	Prolonged diastolic relaxation time, Myocardial stiffness Impaired relaxation
Abnormal fatty acid metabolism	Increased systemic lipolysis Loss of metabolic flexibility Increased utilization of FFA	Cardiac steatosis Lipotoxicity Myocyte apoptosis	Increased O_2 consumption, Pathologic cardiac remodeling, Systolic dysfunction
Hyperglycemia	Activation of protein kinase C pathways Production of free radicals	Myocardial necrosis, Dystrophic calcification	Myocardial fibrosis Left ventricular hypertrophy Diastolic dysfunction
Myocardial fibrosis	Transforming growth factor–β Matrix metalloproteinase-2 Smooth muscle actin	Interstitial fibrosis Left ventricular hypertrophy Intimal thickening of microvasculature	Diastolic dysfunction Systolic dysfunction
AGE/RAGE	Janus kinase pathway Mitogen-activated protein kinase (MAPK) pathway activation	Cross-linking of ECM Reduction of myocardial compliance Myocardial fibrosis	Prolonged isovolumetric relaxation time Elevated left ventricular end-diastolic diameter
Reactive oxygen species	Diacylglycerol Protein kinase C NPADH-oxidase pathway	Oxidative myocardial injury Mitochondrial damage Cardiac fibrosis	Myocardial stiffness Diastolic dysfunction
Inflammation	NF-κB, TNF-alpha IL-6	Inflammatory myocardial injury	Systolic dysfunction
CAN	Hyper adrenergic state Increased activation of beta-receptors and RAAS activation	Interstitial fibrosis	Diastolic dysfunction
Deranged protein homeostasis	Impaired ubiquitin proteasome system	Proteotoxicity, myocardial cell damage	Pathological remodeling in diabetic hearts of animals
Microvascular dysfunction	Upregulation of VEGF pathway	Fibrosis of capillaries	Impaired myocardial functional reserve

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, TNF-alpha: Tumor necrosis factor-alpha, IL: Interleukin, RyR: Ryanodine receptor, ECM: Extracellular matrix, FFA: Free fatty acid, VEGF: Vascular endothelial growth factor, RAAS: Renin–angiotensin–aldosterone system.

dependent mechanisms lead to cell infiltration of leucocytes including macrophages and neutrophils and upregulation of inflammatory pathways mediated through Toll-like receptors that play an important role in cardiac inflammation and pathogenesis of metabolic cardiomyopathy. These pathways lead to significant myocardial injury and have been elucidated in the development of chronic dilated cardiomyopathy in DM.[29]

Cardiac autonomic neuropathy (CAN) and role of the renin-angiotensin-aldosterone system (RAAS)

Considerable evidence indicated that CAN has been independently associated with LV dysfunction in asymptomatic patients with type 2 DM without any history of CVD.[30] CAN is associated with imbalance between sympathetic and parasympathetic components of the autonomic nervous system. In early stages parasympathetic denervation is evident, leading to a dominant sympathetic tone,[31] which promotes the release of high myocardial catecholamine levels and activation of adrenergic receptors. This also promotes the increased activation of the systemic and tissue RAAS activity in addition to hyperglycemia. These abnormalities promote interstitial fibrosis, and diastolic dysfunction seen in DCM.[32]

Deranged protein homeostasis

Intra-cellular metabolic activity of myocardial cells can generate misfolded and oxidized protein. The ubiquitin proteasome system is an intracellular protein quality control system that degrades these

Table 4
Studies showing the prevalence of asymptomatic LV dysfunction in patients with DM.

Year	Journal	Total diabetic population	Prevalence of diastolic dysfunction	Main findings
2001	American Journal of Cardiology[42]	86	47%	Valsalva maneuver with Doppler echo and pseudonormal pattern increases the prevalence of diastolic dysfunction
2001	Diabetes Care[69]	46	60%	Screening for LV diastolic dysfunction in type 2 DM using Valsalva maneuver and pulmonary venous recordings unmasks pseudonormal pattern of ventricular filling
2004	American Journal of Cardiology[45]	61	75%	Prevalence of LV diastolic dysfunction in asymptomatic, normotensive patients with type 2 DM without evidence of CAD is significantly higher with addition of Tissue Doppler Imaging
2008	Diabetes, Obesity and Metabolism[70]	42	28%	Significant association between diastolic and microvascular dysfunction
2010	Circulation: Cardiovascular Imaging[71]	305	40%	Asymptomatic type 2 diabetic patient with no cardiovascular disease have high prevalence of diastolic dysfunction while a low prevalence of LV systolic dysfunction (9%) seen similar to the prevalence observed in the general population
2011	Journal of Cardiovascular Disease Research[72]	127	54.33%	Prevalence of diastolic dysfunction in asymptomatic diabetic correlates with the duration of diabetes, HbA1c levels and presence of diabetic microangiopathies
2013	National Journal of Medical Research[73]	50	66%	High prevalence of diastolic dysfunction in diabetes, which is an early marker of DCM
2014	Journal of Cardiac Failure[74]	2042	54%	1.7 folds increase in risk of diastolic dysfunction, and a 2.2 folds increase in risk of systolic dysfunction
2017	Hypertension[75]	899	33%	2D color Doppler used to study diastolic dysfunction. Diabetic patients have higher prevalence of diastolic dysfunction compared to patients with hypertension

LV: Left ventricle, DM: diabetes mellitus, CAD: Coronary artery disease, DCM: diabetic cardiomyopathy, A1C: Hemoglobin A1c, 2D; 2 dimensional.

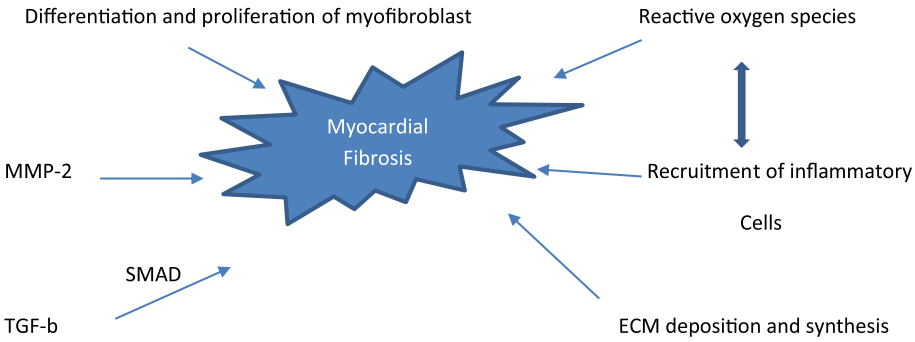

Fig. 4. Schematic diagram depicting the various pathways involved in myocardial fibrosis. MMP-2: Matrix metalloproteinase-2, TGF-b: transforming growth factor-beta, ECM: extracellular matrix.

proteins. Impairment of this vital mechanism leads to impairment of cardiac contractility, maladaptive cardiac remodeling in animal models of HF.[33] The exact pathophysiological mechanism of ubiquitin proteasome system in DCM is unknown. However, the findings of animal studies suggest a potential avenue for therapeutic targets in DCM that might reduce proteotoxicity.

Microvascular dysfunction

Coronary microvascular dysfunction is associated with impaired myocardial functional reserve in the absence of significant anatomic CHD.[34] It involves functional alteration of myocardium resulting from proliferation and fibrosis of capillaries. Hyperglycemia induced production of AGE and decreased production of NO in coronary endothelial cells lead to upregulation in endothelial vascular growth factor.[35] The DM microvascular disease is an independent player in development of subclinical and overt DCM and is a predictor of poor prognosis for subsequent CVD events.

Diagnostic modalities for DCM

Cardiac biomarkers

A wide spectrum of cardiovascular biomarkers has been described in patients with DM. Some of these biomarkers include brain natriuretic peptide (BNP), cardiac troponins and MMPs. Alterations in the levels of these biomarkers can suggest myocardial structural and functional dysfunction. Elevated levels of BNP have been found to show positive correlation with LV dysfunction. In asymptomatic patients BNP can be useful to screen DM patients for the presence of subclinical LV dysfunction.[36]

Cardiac troponins (T, N, and I) are released into the circulation from the injured myocardium in inflammatory or ischemic disease. Mildly elevated levels of highly-sensitivity circulating cardiac troponins have been found in untreated type 2 DM patients independent of traditional CVD risk factors.[37] However, the role of troponins for the assessment of adult patients with DCM is unclear. Future studies are required to determine whether cardiac troponins can be used as biomarkers for early diagnosis of subclinical myocardial injury.

MMPs are enzymes that are involved in metabolism of extracellular matrix. Elevated levels of MMPs, especially MMP-9, and reduced levels of the tissue inhibitors of MMPs, are observed in myocardial fibrosis. The predictive role of these biomarkers in patients with CVD and DM are still not clear because of limited evidence.

Cardiac imaging

Doppler echocardiography

Echocardiography is a standard modality to diagnose DCM. It involves detecting structural and functional changes in the LV and excluding other CVD that could be the potential reason for those changes in a patient with DM. Comprehensive evaluation of DCM with standard transthoracic Doppler echocardiography involves the assessment of diastolic dysfunction, LV filling pressure and myocardial perfusion reserve.

Glucose impairment is independently associated with abnormal diastolic filling, an effect which is pronounced in the presence of HTN.[38] LVH and myocardial fibrosis are the earliest morphological alterations that are seen in patients with pre-DM and early DM stages, which result in diastolic dysfunction. Pulsed-wave transmitral Doppler is used to detect diastolic function. The impaired LV relaxation results in reduced early and prolonged late diastolic flow.[39] With time, these patients progress to advanced stages of diastolic dysfunction characterized by rapid early diastolic filling and rapid velocity deceleration. In between early and late diastolic dysfunction is pseudonormal pattern where Doppler echocardiography can be normal but can be differentiated by Valsalva maneuver and pulmonary venous flow. Transmitral E/A ratio has been established as a reliable marker to predict prognosis.[40] Few observational studies have demonstrated the abnormal E/A ratio in asymptomatic, normotensive patients with type 2 DM, suggesting some degree of diastolic dysfunction.[41] Another study reported that 30% of DM patients, who are asymptomatic and normotensive, have diastolic dysfunction.[42] Although Doppler echocardiography is a prime modality for initial assessment of patients with DM, it has limitations and is not ideal, and the addition of Tissue Doppler Imaging (TDI) improves its diagnostic accuracy.

Color M-mode Doppler

Color M-mode Doppler echocardiography is preload independent[43] in comparison to Doppler echocardiography for the detection of diastolic dysfunction and LV filling pressures. It measures mitral inflow jet velocity from annulus to apex to measure LV relaxation. Tachycardia and dilated chambers can be limiting factors, however, in the utility of M-mode Doppler.

Role of Tissue Doppler Imaging (TDI)

There has been emergence of TDI to assess myocardial velocities as a result of long-axis motion of the LV. It is employed to detect DM- related diastolic dysfunction and increased LVEDP in patients with normal systolic function. Especially in patients with normal E/A ratio (pseudonormal pattern) on Doppler echocardiography, TDI is a reliable parameter of diastolic dysfunction. Tissue Doppler E/E′, which is the ratio of transmitral flow to mitral annular velocity, is a marker of assessment of increased LVEDP and it has been correlated with glycated hemoglobin (HbA1C) levels and hence glycemic control in patients with diastolic dysfunction.[44] In a study by Boyer et al including patients with DM, 46% were diagnosed with diastolic dysfunction by Doppler echocardiography and the percentage increased to 74% after addition of TDI.[45] Left atrial volume index is also independently associated with the degree of diastolic dysfunction.[46] In another study by Bonito

et al,[47] half of the patients with normal diastolic function by standard Doppler echocardiography had abnormal TDI velocities, suggesting diastolic dysfunction. One of the limitations to detect diastolic dysfunction by TDI, however, is the presence of adjacent abnormal myocardial segment which can affect the measurement of velocities.

Role of speckle tracking echocardiography

Speckle-tracking derived strain can be used for early detection of LV dysfunction during the progression of DM. Studies of animal models have demonstrated that speckle-tracking based strain analysis is a very sensitive method that helps in the early detection of global changes in LV function in comparison to those seen in conventional echocardiography in early DM. Reduction in both circumferential and longitudinal strain rate can be visible as early as the first few weeks post-DM onset.[48] Early detection of these subtle changes can help clinicians to prevent further progression of DCM.

Subclinical LV longitudinal dysfunction is preferentially and frequently observed in asymptomatic DM patients with normal EF on speckle echocardiography. Speckle derived global longitudinal and radial strain measurements can increase the detection of subclinical DCM.[49] Strain can also be used to evaluate segmental cardiac dysfunction and allows for regional assessment as well. These findings can be used for risk stratification of asymptomatic patients with DM.

Cardiac magnetic resonance imaging (MRI)

Extracellular matrix expansion and interstitial fibrosis is one of the important pathological features in patients with DCM, and MRI has been found superior to other imaging modalities in the identification of cardiac scars or local fibrosis. In MRI, various imaging techniques can be employed to evaluate the extent of fibrosis. One of the most commonly used techniques is contrast enhanced magnetic resonance imaging using gadolinium. Late-gadolinium enhancement (LGE) MRI has been used extensively in a large number of studies for measurement of myocardial scarring.[50] The physiological basis of the LGE in myocardial fibrosis is based on prolonged retention of gadolinium-contrast agent in myocardial tissue secondary to delayed washout related to the decreased capillary density within the myocardial fibrotic tissue.[51] Recent studies show the defining role of LGE in assessing myocardial fibrosis for prognostic purposes in patients with DCM without any evidence of underlying CHD. Patients with DM with occult myocardial scarring have been found to be high risk of future CVD events.[52] This finding suggests that MRI can help to identify a subpopulation of DM patients who may benefit from more intensive medical management.

T1 mapping is another recently used MRI technique for assessment of DCM.[53] T1 mapping directly measures variation in intrinsic myocardial tissue properties which allows the identification of myocardial pathology that is global, such as diffuse myocardial fibrosis that can be seen in patients with DCM. LGE relies on the regional segregation of tissue characteristics and can detect only regional abnormalities, such as local scar tissues, which differentially accumulates gadolinium contrast agent. Thus, myocardial pathology that is diffuse in nature and affecting the myocardium in a rather uniform and global distribution is not well visualized with LGE.[54] In that case, T1 mapping can be used to measure diffuse myocardial fibrosis and differentiate between disease processes. T1 mapping can also help to qualify extracellular volume expansion, which has been shown to be significantly correlated with impaired LV diastolic function.[55]

Nuclear imaging

Radionuclide ventriculography (RNV) uses technetium labelled red blood cells and has been used to measure diastolic and systolic ventricular function parameters such as LVEF, LV end- diastolic volume, LV end-systolic volume and peak filling rate. Sasso et al studied the effects of insulin resistance on LV function and found that metabolic impairment plays a significant role in development of LV dysfunction in DCM.[56]

Gated Single Photon Emission Computed Tomography

Gated Single Photon Emission Computed Tomography (G-SPECT) provides simultaneous assessment of LV function and myocardial perfusion with a single test. By allowing the measurement of LVEF, G-SPECT yields information about myocardial function when evaluating cardiac perfusion status. It also allows assessment of wall thickening and motion that has been shown to increase both the sensitivity and specificity of myocardial perfusion imaging. However, to date, there has been no studies to define which group of patients with DM are good candidates for G-SPECT and will benefit from this imaging modality in either human or experimental models.[56]

Positron emission tomography (PET)

In contrast to G-SPECT, PET can assess myocardial blood flow and helps in the estimation of coronary flow reserve. Patients with DCM can have significant impairment of coronary microcirculation that is seen across the spectrum of various degrees of insulin resistance and can be assessed by PET. Fluoro-deoxyglucose PET scan has also been used in studies that correlate assessment of myocardial dysfunction with myocardial substrate metabolism.[57] A recent study shows that shifts of myocardial substrate metabolism towards higher fatty acid oxidation are associated with concomitant LV dysfunction in both in vitro and in vivo settings in animal models.[58] In asymptomatic patients with type 2 DM, PET scan does not show any direct relation between diastolic dysfunction and metabolic parameters, even though it did show an increase in myocardial fatty acid metabolism in type 2 DM patients.[59] The disadvantage of PET scan that sets back its utility in clinical practice is its prohibitive cost.

Role of endomyocardial biopsy

Several pathological changes have been demonstrated in endomyocardial biopsy (EMB) specimens of DM patients with impaired LV function. These changes have been seen irrespective of the presence or absence of HTN. Interstitial fibrosis, thickening of capillary basement membranes, intimal thickening and subendothelial fibroblastic proliferation have been demonstrated.[60,61] Molecular analysis of pathology specimens shows increased deoxy ribonucleic acid (DNA) breakdown in cardiac myocytes leading to apoptosis.[62] This progressive loss of cardiac myocytes via apoptosis leads to progressive transition from compensated to decompensated LV dysfunction in the DM heart and plays an important role in development of DCM.[63] Interstitial fibrosis and myocyte hypertrophy is seen in early stage of DCM with preserved systolic function that leads to more restrictive physiology. With progressive myocardial damage resulting from apoptosis, extracellular matrix deposition and fibrotic remodeling, it progresses towards more systolic HF with DCM.[64]

Clinical perspectives of DCM

Epidemiology

There is consistent epidemiological evidence that DM is common in patients with HF.[65] In fact, the most common CV complication in patients with DM is HF. In the major HF trials, DM patients often represent most of study subjects. Cardiomyopathy does not occur only in DM patients, but rather in pre-DM patients with metabolic syndrome who have elevated inflammatory markers and microalbuminuria associated with incident HF. Patients with DM and HF have increased mortality compared to non-DM patients even after adjustment of clinically recognized potential confounders. These patients not only have increased mortality but also present with recurrent hospitalizations from HF. A 1% increase in the baseline level of HbA1c increased the risk of developing HF by 15% in patients with and without known DM.[66] This indicates that the independent risk for developing HF in DM patients may to some extent be mediated by poor metabolic control. Many patients diagnosed with idiopathic cardiomyopathy have underlying DM, and this

association is independent of age, race, HTN and other confounding variables.[67] Another study showed that DM was present in 22% of patients with idiopathic cardiomyopathy compared to 11% in the control group.[68] The prevalence of underlying LV dysfunction in DM patients varies according to duration of DM, levels of HbA1C in DM cohorts, and techniques used to evaluate diastolic dysfunction. This is shown by the relatively low prevalence of diastolic dysfunction in older studies compared to new studies that used more advanced echocardiographic imaging techniques, such as TDI. Table 4 shows the prevalence of diastolic dysfunction in asymptomatic type 2 DM population in various studies done after 2000.

Risk factors

The three major risk factors for development of DCM are hyperglycemia, hyperinsulinemia and insulin resistance. In patients enrolled in the national Swedish registry, analysis of 20, 985 DM patients, the hazard ratio for development of HF was 3.98 in patients with $HbA_{1c} \geq 10.5\%$ compared to the reference group of patients with $HbA_{1c} < 6.5\%$, even after adjustment for age, sex, duration of DM, CVD risk factors, and other comorbidities.[76] The pathophysiology of DCM supports the fact that patients with high HbA1C levels have increased accumulation of advanced glycation products that is a strong contributor to myocardial fibrosis.[24] Therefore, the extent and frequency of diastolic dysfunction was directly proportional to the HbA1c level in the Strong Heart Study.[77] Similarly, in another study, patients with HbA1c > 7.5% had a higher prevalence of diastolic dysfunction than those with HbA1c < 7.5%. Reduction in HbA1C levels reduced the risk of developing HF.[78] In fact, the risk of HF increases further with age and duration of DM.[71] Assessment of these factors should help a primary care physician in making an early diagnosis of underlying LV dysfunction in DM patients.

Screening for DCM

The majority of patients with DCM have asymptomatic LV dysfunction in the initial stages. Many of these patients with LV dysfunction remain undiagnosed and untreated at Stage A of HF. Identification of these patients at early stages can help identify patients at high risk for further progression of disease. This necessitates the development of screening tests to identify those patients who are at increased risk.

The role of BNP has been studied for screening asymptomatic DM patients. BNP is a simple, rapid and cost-effective screening test. However, multiple studies have failed to demonstrate that BNP can provide sufficiently sensitive clinical information to identify subclinical dysfunction. In these studies, BNP proved to be a suboptimal screening test to detect pre-clinical LV dysfunction or LVH.[79,80,81] Similarly, high sensitivity C-reactive protein was also not found to be an effective screening method, either alone or in combination with BNP to identify preclinical DCM.[81]

Microalbuminuria performed annually in DM patients can help risk stratify the DM patient at risk for having underlying diastolic dysfunction. Persistent microalbuminuria can be used as markers of diffuse fibrosis and diastolic dysfunction as shown in a recent study.[82] This study shows that cardiac extracellular volume which quantifies myocardial fibrosis is higher in DM patients compared to controls, and even higher in patients who test positive for microalbuminuria. These results are in concordance with the results of Strong Heart Study which showed that the degree of diastolic dysfunction is proportional to the level of microalbuminuria, even after adjusting for age, sex, and body mass index (BMI), systolic blood pressure, and duration of DM, LVM, and presence of CHD.[77]

The most sensitive test, however, continues to be echocardiography with Doppler techniques, as shown by most of the studies. Routine use of echocardiography in daily clinical practice is not cost-effective in this scenario. Therefore, assessment of individual risk factors becomes very important in clinical practice especially in primary care settings. Patients with compatible history, such as poor glycemic control (HbA1C > 9), insulin dependent DM, longer duration of DM (>5 years) and other CVD risk factors, such as HTN and hyperlipidemia, should be evaluated for screening by echocardiography.[83]

Novel therapies for treatment of DCM

Role of antioxidants

Hyperglycemia induced oxidative stress is a major risk factor in development of myocardial dysfunction in DCM as explained above. Multiple studies have evaluated the role of antioxidants, including vitamin E, Metallothionein, synthetic glutathione peroxidase and multiple other antioxidant approaches.[84] The efficacy of these agents has been studied in animal models with DM. These agents have shown to have cardio protective effects in animal models, suggesting the usefulness of vitamin E supplementation during the early phases of type 1 DM for the prophylaxis of cardiomyopathy and subsequent HF.[85] However, most of the placebo controlled randomized clinical trials have failed to show any true efficacy of supplementary vitamin E therapy in DM patients at risk.[86] The possible etiologies of these could be failure to measure biomarkers of oxidative stress and subsequent lack of ability to tailor the dose of antioxidants to achieve adequate suppression at the levels of oxidative stress in relation to the dose of antioxidants.[87] New insights into the mechanisms that increase oxidative stress in DM might lead to development of novel treatment strategies. Further human studies that could address these problems will be needed to document any significant protective effects of these agents.

Coenzyme 10 (CoQ 10)

Recently CoQ 10 supplementation has been shown to reduce oxidative stress in DM mice. Three months after induction of DM in animal model, adverse cardiac remodeling is significantly attenuated in mice who received CoQ 10.[88] The role of CoQ 10 supplementation as adjunctive therapy has been supported by recent multiple small heterogeneous studies and a recent relatively large randomized multicenter trial which showed that long term treatment of patients with chronic HF reduced major adverse CVD events and has shown mortality benefit.[89] CoQ 10 has not been shown to have significant adverse effects as well. However further studies are needed to support its widespread use and ensure the safety of this drug.

Phosphoinositide3-kinase gamma (PI3Kg) inhibitor

PI3Kg has been evaluated in animal models and seems to play a key role in the development of cardiac dysfunction in DM rats.[90] Accordingly, pharmacological inhibition of PI3Kg can revert the cardiac dysfunction induced by DM. PI3Kg inhibitors, however, have a very slow onset and take a long duration to show their positive effects. Their effect will need to be validated in future studies to determine their potential use for treatment of human DCM.

Role of MicroRNA

MicroRNAs (miRNAs) are short noncoding RNAs that modify gene expression by regulating mRNA stability or translation during various disease processes. Each mRNA regulates expression of multiple genes. Dysregulated miRNAs are potentially involved in the pathogenesis of DCM.[91] There are multiple miRNAs that have been implicated with the progression of disease. Modulating the expression of miRNA by either a mimic or an inhibitor in animal models has been shown to reverse histologic and functional measures of cardiomyopathy.[92] Therefore, this has potential to ameliorate DCM. Thus, miRNA-based therapies may provide value in DM patients with cardiac pathology in the future. Further investigations are required for better understanding of the

mechanisms involved in crosstalk between miRNA and gene expression to use these as novel therapeutic targets in DCM.

Visceral adipose tissue–derived serine protease inhibitor (Vaspin)

Vaspin is an adipocytokine that can prevent TNF-alpha associated myocardial injury by inhibiting apoptosis in patients with DCM. TNF-alpha associated pathways inhibit autophagy in cardiac myocytes and promote apoptosis. By inhibiting these pathways, this novel agent can significantly reduce myocardial apoptosis, which plays a significant role in development of contractile dysfunction.[93]

Role of dietary medium-chain fatty acids

One small double-blind, randomized, 2-week matched-feeding study reported that medium-chain fatty acids (MCFAs) diet may be beneficial for cardiac function in patients with type 2 DM. This study did not show any effect on myocardial structure or lipid deposition in the myocardium. However, there was improvement in indirect measures of myocardial contractility such as Doppler derived S′ wave velocity. There was no effect on stroke volume or cardiac output noted in patients taking MCFAs. However, it was a small study and further larger studies are needed to validate these fatty acids.[94]

Stem cell therapy in DCM

Cardiac stem cells are the progenitor cells that have the ability to differentiate into cardiac myocytes.[95] Patients with DCM have progressive loss of cardiac myocytes because of various injury mechanisms and inability to replace them because of low regenerative potential. Stem cells can be used to replace those lost myocytes. They are also helpful in DCM patients with microvascular dysfunction with their ability to differentiate endothelial cells and promote neo revascularization.[96] Thus, stem cells are promising for the treatment of DCM. However, their role has been demonstrated only in animal models so far. Therefore, further studies evaluating the role of this unique therapy in humans are needed.

Conventional therapies

Angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs)

ACEI and ARBs significantly reduce the risk of developing myocardial fibrosis and LV stiffness. The beneficial role of ACEI/ARBs in DCM results from their role in reverting the development of abnormal extracellular matrix deposition and fibroblast activity by decreasing the synthesis of collagen and increasing activity of MMP.[97] They also modulate the response of cardiac myocytes to sympathetic system and RAAS and downgrade the development of LVH and cardiac remodeling. In multiple observational studies and randomized trials, ACEI have been shown to reduce both all- cause and CVD mortality in DM patients with overt HF and those with asymptomatic LV dysfunction without heart failure.[98]

Angiotensin receptor–neprilysin inhibitor (ARNi)

ARNi is a combination of angiotensin receptor inhibitor and neprilysin inhibitor. This agent has been shown to attenuate the abnormal cardiac remodeling and fibrotic changes in animal model of DCM.[99] After 4 weeks of therapy with ARNi, there is significant improvement in left ventricular ejection fraction in treatment group vs control group. At the molecular level, the levels of TGF-b are significantly decreased which is demonstrated by significant reduction in myocardial fibrosis. The mechanism by which neprilysin inhibitor reduces fibrosis likely involves inhibition of angiotensin II-dependent and TGF-dependent fibrotic processes with reduction of pressure induced cardiac remodeling. ARNi are being used as a second line agent in patients with HFrEF who continue to be symptomatic despite being on ACEi/ARBs and aldosterone antagonists. Many of these patients have also diabetes as well. Since DCM is a unique clinical entity, there is need for randomized controlled trials specifically in this patient population to assess the long term benefits of ARNi.[100]

Beta-blockers (BBs)

BBs reduce the risk of HF hospitalization and mortality in patients with HFrEF.[101] These drugs have been shown to prevent and reverse many of the structural and functional changes that occur during the progression of HF by preventing the toxic effects of catecholamines. BBs, such as carvedilol, exert anti- adrenergic effect and reduce sympathomimetic effects in patients with DCM. In addition, they also pose antioxidant and antiendothelin effects that provide favorable effects in preventing LV dysfunction.[102] As a matter of fact, long term administration of BBs can improve the LVEF by increasing stroke volume, decreasing pulmonary capillary wedge pressure, right atrial pressure and systemic vascular resistance.[103] Combined ACEI and BBs exert extremely important neurohormonal effects to provide first line therapeutic options for patients with DCM.

Aldosterone antagonists (AAs)

Aldosterone is an important instigator of myocardial fibrosis. It also shifts the autonomic balance towards the sympathetic nervous system. By blocking aldosterone receptors, spironolactone increases the reuptake of nor-epinephrine by myocardial cells. Studies have shown that spironolactone reduces serum levels of procollagen peptides and decreases myocardial collagen turnover, reducing vascular damage and myocardial fibrosis.[104] The beneficial effects of AAs have been demonstrated in the RALES trial that showed treatment with spironolactone reduces CVD mortality, all-cause mortality and HF hospitalizations in patients with stage III and IV HF and LV dysfunction in addition to standard therapy with ACEI.[105] Given the clinical efficacy of these agents in DM patients with HF, therapy with ACEI, BBs and AAs for patients with advanced NYHA class III-IV HF is indicated. However, since patients with DM have sclerosis of the juxta-glomerular apparatus and baseline type-4 renal tubular acidosis, these patients may be more susceptible than non-DM patients to significant hyperkalemia.[106]

Role of anti-glycemic agents in DCM

Incretin-based therapies (IBT)

IBT include Glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors for the treatment of DM. These agents exert their CV effects both indirectly through their actions on myocardial metabolism and direct functional effects on cardiac myocytes and coronary vasculature.[107] The metabolic effects result from an increase in insulin levels and a decrease in glucagon levels with concomitant decrease in levels of circulating free fatty acids. This enhances the glucose uptake in cardiac myocytes and at the same time decreases fatty acid utilization. Both of these metabolic effects improve myocardial metabolism and halt the abnormal metabolic pathways leading to contractile dysfunction as explained in the pathophysiological pathways of DCM above. These agents also decrease inflammatory pathways in myocardial cells and reduce inflammatory myocardial damage. GLP-1 receptors are expressed on vascular smooth muscles and endothelial cells. Direct effect on these cells promotes coronary blood flow and increases glucose uptake.

The role of these agents in patients with HF, however is limited. Systemic treatment with GLP-1R agonists and DDP-4 inhibitors exert beneficial effects on LV function in pre-clinical studies, but these are

contrasted with modest and often inconclusive results in short-term human studies.[108] In a study of 20 patients with NYHA class II and III HF, 48-h GLP-1 infusions did not improve myocardial contractile function or BNP levels (111), which is in contrast to findings reported in other studies that showed treatment with GLP-1 agents improved LVEF (112). Similarly, regarding DDP-4 inhibitors, a study with 254 patients with type 2 DM and NYHA class I, II, or III HF treated with vildagliptin reported increases in LV end-diastolic and LV end-systolic volume (113). Further studies are needed to assess the safety and efficacy of these agents in patients with DCM.

Metformin

Metformin has been thought to be contraindicated in DM patients with HF because of its potential to cause lactic acidosis. However, recent evidence suggests that metformin has several favorable effects on the pathophysiology of DCM by reducing insulin resistance.[112] Metformin has been shown to reduce the risk of HF and mortality in DM patients.[113] Results of animal studies show that metformin increases the activity of endothelial NO and AMPK protein kinase pathway, reduces activity of TNF-alpha and fibroblast growth factor, thus reducing LV volume and LV remodeling, hence improving systolic and diastolic parameters.[114] However, metformin should be stopped in patients with acutely decompensated HF, sepsis or hypoperfusion settings to avoid lactic acidosis.

Thiazolidinediones (TZDs)

In vitro and animal studies suggest that TZDs can reduce the serum levels of MMP-9 and the proinflammatory marker CRP in patients with type 2 DM. These drugs exert their effects by activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) and promote anti-inflammatory effects by inhibiting inflammatory cells.[115] However, the use of these agents in clinical practice is limited mainly because of their potential to cause edema and HF. These drugs also have the propensity to promote weight gain, and obesity increases the risk of HF.[116] Similarly, patients on these drugs had increased incidence of HF compared to control. In trials validating the use of these drugs, patients with advanced Class III, IV HF were excluded. Therefore, these agents should not be used in patients with significant HF and caution should be used in patients who already have any signs or symptoms of HF.[117]

Sulfonylureas

Sulfonylureas are commonly used in patients with DM. Studies comparing metformin versus sulfonylurea[118] showed metformin has beneficial effects, but sulfonylureas do not. These drugs have significant impact on weight and increase BMI and, therefore, increase the risk of HF. In a study done in a veteran's population, sulfonylurea initiation was associated with an increased risk of HF hospitalization and CVD death compared with metformin initiation.[119] These drugs also cause significant hypoglycemia as well. Given the clinically important increase in HF and other CVD risk associated with sulfonylureas compared with metformin, other drugs could be considered instead of sulfonylureas for those intolerant to metformin or needing additive therapy.

Sodium-glucose transporter-2 (SGLT-2) inhibitors

Recently SLGT-2 inhibitors have been suggested as first line drugs to achieve glycemic control in DM patients with HF. In comparison to other agents, these drugs have been shown to reduce the rate of HF related admission in DM patients and lower CVD mortality in a placebo controlled randomized clinical trial.[120] The exact mechanisms of these benefits are not well understood yet. Further studies are underway to explain how these drugs provide these benefits. These drugs have lower the risk of hypoglycemia compared to sulfonylurea and do not induce weight gain as well. Results of further studies will help define the exact pathways implied in HF progression targeted by these drugs and could potentially become standardized treatment for HF diabetic patients.

Conclusions

DCM is more common than it is recognized clinically. It is an important cause of HF worldwide and constitutes a significant burden of health care cost across the nation. The pathophysiology of DCM is complex and despite significant advances, many areas are still not well understood and are target for future studies. Taken together, there are underlying pathological changes resulting from multiple abnormal biochemical pathways ranging from abnormal calcium signaling, deranged glucose/fatty acids metabolism and inflammatory pathways that result in myocardial fibrosis, stiffness and hypertrophy. The clinical effects of these are progression from asymptomatic diastolic dysfunction to systolic dysfunction and clinical HF. In order to halt this natural progression of disease, screening and early diagnosis is extremely important. Many of these asymptomatic patients are being managed in primary care settings; therefore, clear understanding of this condition on part of primary care physicians is important to allow early assessment of myocardial performance and subclinical damage. There is no single biomarker or definitive screening test available, and assessment of risk factors, clinical history and physical exam is useful for making decisions regarding screening of DCM. The risk of DCM does not stem only from hyperglycemia or hyperinsulinemia, but multiple other factors, including obesity, HTN and CHD as well. The control of hyperglycemia is important though intensive glucose control has not been shown to have any beneficial effects on risk of developing clinical HF. Similarly, an intensive lifestyle intervention focusing on weight loss did not reduce the rate of CVD events in overweight or obese adults with type 2 DM.[121] In patients with diastolic dysfunction, control of blood pressure and heart rate is important. In those with advanced systolic dysfunction, BBs, ACEI/ARBs and AAs are the cornerstone of therapy, although the risk of hyperkalemia must be considered and assessed. There are novel therapies being developed, including miRNA and stem cell therapies, in treatment and prevention of DCM. However, further studies are needed to fully understand the precise mechanisms involved in the progression of disease and to continue the development of novel therapies to reduce the risk of developing DCM.

Disclosures/Conflict of interest

The authors report no financial relationships or conflicts of interest regarding the content herein.

References

1. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 1972;30:595-602.
2. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29-34.
3. Aneja A, Tang WH, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. Am J Med 2008;121(9):748-757.
4. Mizamtsidi M, Paschou SA, Grapsa J, Vryonidou A. Diabetic cardiomyopathy: a clinical entity or a cluster of molecular heart changes? Eur J Clin Investig 2016 Nov;46 (11):947-953 https://doi.org/10.1111/eci.12673.
5. Boudina S. Clinical manifestations of diabetic cardiomyopathy. Heart Metab 2009;45:10-14.
6. Aneja A, Tang WW, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. Am J Med 2008; 121:748–57?
7. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy an update of mechanisms contributing to this clinical entity. Circ Res 2018;122:624-638 https://doi.org/10.1161/CIRCRESAHA.117.311586.
8. Redfield MM, Jcobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community. JAMA 2003;289: 194-202.

9. Jia G, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. Nat Rev Endocrinol 2016;12:144-153 https://doi.org/10.1038/nrendo.2015.216.
10. Bertero E, Maack C. Calcium Signaling and Reactive Oxygen Species in Mitochondria. Circulation Research. 2018; 122:1460–1478. https://doi.org/10.1161/CIRCRESAHA.118.310082.
11. Jiang X, Liu W, Deng J, et al. Polydatin protects cardiac function against burn injury by inhibiting sarcoplasmic reticulum Ca2+ leak by reducing oxidative modification of ryanodine receptors. Free Radic Biol Med 2013;60:292-299.
12. Pierce GN, Ramjiawan B, Dhalla NS, Ferrari R (1990) Na+ -H+ exchange in cardiac sarcolemmal vesicles isolated from diabetic rats. Am J Phys 258:H255–H261?
13. Makino N, Dhalla KS, ElimbanV DNS (1987) Sarcolemmal Ca2+ transport in streptozotocin-induced diabetic cardiomyopathy in rats. Am J Phys 253:E202–E207?
14. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiol Rev 2010 Jan;90(1):207-258.
15. Herrero P, Peterson LR, McGill JB, et al. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. J Am Coll Cardiol 2006 Feb 7;47(3):598-604.
16. Carley AN, Severson DL. Fatty acid metabolism is enhanced in type 2 diabetic hearts. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2005 May 15; 1734(2):112–26.
17. Falcão-Pires I, Hamdani N, Borbély A, et al. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. Circulation 2011;124:1151-1159.
18. Wu LM, Wu R, Ou YR, et al. Fibrosis quantification in hypertensive heart disease with LVH and non-LVH: findings from T1 mapping and contrast-free cardiac diffusion-weighted imaging. Sci Rep 2017;7:559.
19. Li CJ, Lv L, Li H, Yu DM. Cardiac fibrosis and dysfunction in experimental diabetic cardiomyopathy are ameliorated by alpha-lipoic acid. Cardiovasc Diabetol 2012 Dec;11(1):73.
20. Iwano M, Kubo A, Nishino T, et al. Quantification of glomerular TGF-beta 1 mRNA in patients with diabetes mellitus. Kidney Int 1996;49:1120.
21. Dennler S., Ten Dijke P. Smad Proteins in TGF-Beta Signaling. In: Schwab M. (eds) Encyclopedia of Cancer. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-16483-5_5364.
22. Tang M, Zhang W, Lin H, Jiang H, Dai H, Zhang Y. High glucose promotes the production of collagen types I and III by cardiac fibroblasts through a pathway dependent on extracellularsignal-regulated kinase 1/2. Mol Cell Biochem 2007;301:109-114.
23. Palomer X, Salvadó L, Barroso E, Vázquez-Carrera M. An overview of the crosstalk between inflammatory processes and metabolic dysregulation during diabetic cardiomyopathy. Int J Cardiol 2013 Oct 9;168(4):3160-3172.
24. Berg TJ, Snorgaard O, Faber J, et al. Serum levels of advanced glycation end products are associated with left ventricular diastolic function in patients with type 1 diabetes. Diabetes Care 1999;22:1186-1190.
25. Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. J Hypertens 2003 Jan 1;21(1):3-12.
26. Volpe CM, Villar-Delfino PH, Anjos PM, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications. Cell Death Dis 2018 Jan 25;9(2):119.
27. Cai L, Kang YJ. Oxidative stress and diabetic cardiomyopathy: a brief review. Cardiovasc Toxicol 2001;1:181-193.
28. Min W, Bin ZW, Quan ZB, Hui ZJ, Sheng FG. The signal transduction pathway of PKC/NF-kappa B/c-fos may be involved in the influence of high glucose on the cardiomyocytes of neonatal rats. Cardiovasc Diabetol 2009;8:8.
29. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236-241.
30. Sacre JW, Franjic B, Jellis CL, Jenkins C, Coombes JS, Marwick TH. Association of cardiac autonomic neuropathy with subclinical myocardial dysfunction in type 2 diabetes. JACC Cardiovasc Imaging 2010 Dec 1;3(12):1207-1215.
31. Axelrod S, Lishner M, Oz O, Bernheim J, Ravid M. Spectral analysis of fluctuations in heart rate: an objective evaluation of autonomic nervous control in chronic renal failure. Nephron 1987;45:202-206.
32. Bernardi S, Michelli A, Zuolo G, Candido R, Fabris B. Update on RAAS modulation for the treatment of diabetic cardiovascular disease. J Diabetes Res 2016;2016.
33. Li J, Ma W, Yue G, et al. Cardiac proteasome functional insufficiency plays a pathogenic role in diabetic cardiomyopathy. J Mol Cell Cardiol 2017 Jan 1;102:53-60.
34. Bratis K, Child N, Terrovitis J, et al. Coronary microvascular dysfunction in overt diabetic cardiomyopathy. IJC Metab Endocr 2014 Nov 1;5:19-23.
35. H.A. Hadi, J.A. Suwaidi Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag, 3 (6) (2007), pp. 853–876.
36. Maisel AS, Koon J, Krishnaswamy P, et al. Utility of B-natriuretic peptide (BNP) as a rapid, point-of-care test for screening patients undergoing echocardiography for left ventricular dysfunction. Am Heart J 2001;141:367-374.
37. McEvoy JW, Lazo M, Chen Y, et al. Patterns and determinants of temporal change in high-sensitivity cardiac troponin-T: the Atherosclerosis Risk in Communities Cohort Study. Int J Cardiol 2015;187:651-657.
38. Liu JE, Palmieri V, Roman MJ, et al. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. J Am Coll Cardiol 2001 Jun 1;37(7):1943-1949.
39. Galderisi M. Can technical limitations of strain rate imaging be overtaken by particular arrangements? J Am Coll Cardiol 2006 Oct 17;48(8):1729.
40. Bella JN, Palmieri V, Roman MJ, et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. Circulation 2002 Apr 23;105(16):1928-1933.
41. Fischer M, Baessler A, Hense HW, et al. Prevalence of left ventricular diastolic dysfunction in the community: results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J 2003 Feb 1;24(4):320-328.
42. Zabalgoitia M, Ismaeil MF, Anderson L, Maklady FA. Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. Am J Cardiol 2001 Feb 1;87(3):320-323.
43. Takatsuji H, Mikami T, Urasawa K, et al. A new approach for evaluation of left ventricular diastolic function: spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography. J Am Coll Cardiol 1996 Feb 1;27(2):365-371.
44. Shishehbor MH, Hoogwerf BJ, Schoenhagen P, et al. Relation of hemoglobin A1C to left ventricular relaxation in patients with type 1 diabetes mellitus and without overt heart disease. Am J Cardiol 2003 Jun 15;91(12):1514-1517.
45. Boyer JK, Thanigaraj S, Schechtman KB, Pérez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. Am J Cardiol 2004 Apr 1;93(7):870-875.
46. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002 Dec 15;90(12):1284-1289.
47. Bonito P, Moio N, Cavuto L, et al. Early detection of diabetic cardiomyopathy: usefulness of tissue Doppler imaging. Diabet Med 2005 Dec 1;22(12):1720-1725.
48. Shepherd DL, Nichols CE, Croston TL, et al. Early cardiac dysfunction in the type 1 diabetic heart using speckle-tracking based strain imaging. J Mol Cell Cardiol 2016;90:74-83 https://doi.org/10.1016/j.yjmcc.2015.12.001.
49. Nakai H, Takeuchi M, Nishikage T, Lang RM, Otsuji Y. Subclinical left ventricular dysfunction in asymptomatic diabetic patients assessed by two-dimensional speckle tracking echocardiography: correlation with diabetic duration. Eur J Echocardiogr 2009 Jul 20;10(8):926-932.
50. Nathan M, Ying LC, Pierre C, David B, João L. Assessment of myocardial fibrosis with cardiac magnetic resonance. J Am Coll Cardiol 2011 Feb 22;57(8):891.
51. Ambale-Venkatesh B, Lima JA. Cardiac MRI: a central prognostic tool in myocardial fibrosis. Nat Rev Cardiol 2015 Jan;12(1):18.
52. Kwong, Raymond Y. et al. "Incidence and Prognostic Implication of Unrecognized Myocardial Scar Characterized by Cardiac Magnetic Resonance in Diabetic Patients without Clinical Evidence of Myocardial Infarction." Circulation 118.10 (2008): 1011–1020. PMC. Web. 16 May 2018.
53. Ellims AH, Shaw JA, Stub D, et al. Diffuse myocardial fibrosis evaluated by post-contrast t1 mapping correlates with left ventricular stiffness. J Am Coll Cardiol 2014;63:1112-1118 https://doi.org/10.1016/j.jacc.2013.10.084.
54. Puntmann VO, Peker E, Chandrashekhar Y, Nagel E. T1 mapping in characterizing myocardial disease: a comprehensive review. Circ Res 2016 Jul 8;119(2):277-299.
55. Shang Y, Zhang X, Leng W, et al. Assessment of diabetic cardiomyopathy by cardiovascular magnetic resonance T1 mapping: correlation with left-ventricular diastolic dysfunction and diabetic duration. J Diabetes Res 2017;2017.
56. Sasso FC, Rambaldi PF, Carbonara O, et al. Perspectives of nuclear diagnostic imaging in diabetic cardiomyopathy. Nutr Metab Cardiovasc Dis 2010 Mar 1;20(3):208-216.
57. Marsh SA, Powell PC, Agarwal A, Dell'Italia LJ, Chatham JC. Cardiovascular dysfunction in Zucker obese and Zucker diabetic fatty rats: role of hydronephrosis. Am J Physiol Heart Circ Physiol 2007;293:H292-H298 https://doi.org/10.1152/ajpheart.01362.2006.
58. van den Brom CE, Huisman MC, Vlasblom R, et al. Altered myocardial substrate metabolism is associated with myocardial dysfunction in early diabetic cardiomyopathy in rats: studies using positron emission tomography. Cardiovasc Diabetol 2009 Dec;8(1):39.
59. Rijzewijk LJ, van der Meer RW, Lamb HJ, et al. Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. J Am Coll Cardiol 2009 Oct 13;54(16):1524-1532.
60. Kawaguchi M, Techigawara M, Ishihata T, et al. A comparison of ultrastructural changes on endomyocardial biopsy specimens obtained from patients with diabetes mellitus with and without hypertension. Heart Vessel 1997 Nov 1;12(6):267-274.
61. Das AK, Das JP. *Endomyocardial Biopsy in Diabetic Cardiomyopathy Procedure, Clinico-Pathological & Structural Functional Correlation.* 1995.
62. Cai L, Kang YJ. Cell death and diabetic cardiomyopathy. Cardiovasc Toxicol 2003 Sep 1;3(3):219-228.
63. Frustaci A, Kajstura J, Chimenti C, et al. Myocardial cell death in human diabetes. Circ Res 2000 Dec 8;87(12):1123-1132.
64. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013 Jul 23;62(4):263-271.
65. Kannel WB. Vital epidemiologic clues in heart failure. J Clin Epidemiol 2000;53:229-235.
66. Chae CU, Glynn RJ, Manson JE, Guralnik JM, Taylor JO, Pfeffer MA. Diabetes predicts congestive heart failure risk in the elderly. Circulation 1998; 98 (Suppl I): 721.
67. Bertoni AG, Tsai A, Kasper EK, Brancati FL. Diabetes and idiopathic cardiomyopathy: a nationwide case-control study. Diabetes Care 2003 Oct 1;26(10):2791-2795.
68. Hamby RI, Zoneraich S, Sherman L. Diabetic cardiomyopathy. JAMA 1974 Sep 23;229(13):1749-1754.
69. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care 2001 Jan 1;24(1):5-10.
70. Brooks BA, Franjic B, Ban CR, et al. Diastolic dysfunction and abnormalities of the microcirculation in type 2 diabetes. Diabetes Obes Metab 2008 Sep 1;10(9):739-746.
71. Patil VC, Patil HV, Shah KB, Vasani JD, Shetty P. Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function. J Cardiovasc Dis Res 2011 Oct;2(4):213.

72. Poulsen MK, Henriksen JE, Dahl J, et al. Høilund–Carlsen PF, Beck-Nielsen H, Møller JE. Left ventricular diastolic function in type 2 diabetes mellitus: prevalence and association with myocardial and vascular disease. Circ Cardiovasc Imaging 2009 Jan 1; CIRCIMAGING-109.
73. Dikshit NM, Wadia PZ, Shukla DK. Diastolic dysfunction in diabetes mellitus. Natl J Med Res 2013;3(3):249-252.
74. Dandamudi S, Slusser J, Mahoney DW, Redfield MM, Rodeheffer RJ, Chen HH. The prevalence of diabetic cardiomyopathy: a population-based study in Olmsted County, Minnesota. J Card Fail 2014 May 1;20(5):304-309.
75. Saxena NR, Saxena J, Saxena A, Srivastava V. *Abstract P355: Prevalence of Diastolic Dysfunction With Preserved Left Ventricular Systolic Function in Hypertensive and Type II Diabetic Patients in a Large Community Practice in Greenville, South Carolina*. 2017.
76. Bounias I, Olsson M, Gudbjornsdottir S, Svenson AM, Rosengren A. Glycaemic control and incidence of heart failure in 20985 patients with type 1 diabetes: an observational study. Lancet 2011;378:140-146.
77. Devereux RB, Roman MJ, Paranicas M, et al. Impact of diabetes on cardiac structure and function: the Strong Heart Study. Circulation 2000;101:2271-2276.
78. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-412.
79. Fang ZY, Schull-Meade R, Leano R, Mottram PM, Prins JB, Marwick TH. Screening for heart disease in diabetic subjects. Am Heart J 2005 Feb 1;149(2):349-354.
80. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction. A community-based study. Circulation 2004;109:3176-3181.
81. Kiencke S, Handschin R, von Dahlen R, et al. Pre-clinical diabetic cardiomyopathy: prevalence, screening, and outcome. Eur J Heart Fail 2010 Sep;12(9):951-957.
82. Swoboda PP, McDiarmid AK, Erhayiem B, et al. Diabetes mellitus, microalbuminuria, and subclinical cardiac disease: identification and monitoring of individuals at risk of heart failure. J Am Heart Assoc 2017 Jul 1;6(7), e005539.
83. Negishi K. Echocardiographic feature of diabetic cardiomyopathy: where are we now? Cardiovasc Diagn Ther 2018 Feb;8(1):47.
84. A Thandavarayan R, V Giridharan V, Watanabe K, Konishi T. Diabetic cardiomyopathy and oxidative stress: role of antioxidants. Cardiovascular & Hematological Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Cardiovascular & Hematological Agents). 2011 Oct 1; 9(4):225–30.
85. Hill MF. Emerging role for antioxidant therapy in protection against diabetic cardiac complications: experimental and clinical evidence for utilization of classic and new antioxidants. Curr Cardiol Rev 2008 Nov 1;4(4):259-268.
86. Liu SM, Lee IM, Song YQ, et al. Vitamin E and risk of type 2 diabetes in the Women's Health Study randomized controlled trial. Diabetes 2006;55(10):2856-2862.
87. Heinecke JW. Is the emperor wearing clothes? Clinical trials of vitamin E and the LDL oxidation hypothesis. Arterioscler Thromb Vasc Biol 2001 Aug 1;21(8):1261-1264.
88. De Blasio MJ, Huynh K, Qin C, et al. Therapeutic targeting of oxidative stress with coenzyme Q10 counteracts exaggerated diabetic cardiomyopathy in a mouse model of diabetes with diminished PI3K (p110α) signaling. Free Radic Biol Med 2015 Oct 1;87:137-147.
89. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, Littarru GP, Q-SYMBIO study investigators. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC: Heart Failure. 2014 Dec 1; 2(6):641–9.
90. Maffei Angelo, Cifelli Giuseppe, Carnevale Raimondo, et al. PI3Kγ inhibition protects against diabetic cardiomyopathy in mice. Rev Esp Cardiol 2017;70:16-24 https://doi.org/10.1016/j.rec.2016.04.034.
91. Quiat D, Olson EN. MicroRNAs in cardiovascular disease: from pathogenesis to prevention and treatment. J Clin Invest 2013 Jan;123(1):11-18 https://doi.org/10.1172/JCI62876.
92. Rodino-Klapac LR. MicroRNA based treatment of cardiomyopathy: not all dystrophies are created equal. JAHA 2013. 2:e000384. https://doi.org/10.1161/JAHA.113.000384.
93. Ke X, Hao Y, Li B, et al. Vaspin prevents tumor necrosis factor-α–induced apoptosis in cardiomyocytes by promoting autophagy. J Cardiovasc Pharmacol 2018 May 1;71(5):257-267.
94. Airhart S, Cade WT, Jiang H, et al. A diet rich in medium-chain fatty acids improves systolic function and alters the lipidomic profile in patients with type 2 diabetes: a pilot study. J Clin Endocrinol Metab 2016 Feb;101(2):504-512.
95. Zhang N, Li J, Luo R, Jiang J, Wang JA. Bone marrow mesenchymal stem cells induce angiogenesis and attenuate the remodeling of diabetic cardiomyopathy. Exp Clin Endocrinol Diabetes 2008;116:104-111 https://doi.org/10.1055/s-2007-985154.
96. Asahara T, Kawamoto A, Masuda H. Concise review: circulating endothelial progenitor cells for vascular medicine. Stem Cells 29(11):1650–1655. doi: https://doi.org/10.1002/stem.745.
97. Brilla CG, Rupp H, Funck R, Maisch B. The renin-angiotensin-aldosterone system and myocardial collagen matrix remodeling in congestive heart failure. Eur Heart J 1995;16:107-109.
98. Flather MD, Yusuf S, Køber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000 May 6;355(9215):1575-1581.
99. Suematsu Y, Miura SI, Goto M, et al. LCZ696, an angiotensin receptor–neprilysin inhibitor, improves cardiac function with the attenuation of fibrosis in heart failure with reduced ejection fraction in streptozotocin-induced diabetic mice. Eur J Heart Fail 2016 Apr;18(4):386-393.
100. Brandenburg VM, Rocca HB, Marx N. Sacubitril/Valsartan in patients with diabetes and heart failure. Deutsche Medizinische Wochenschrift (1946). 2016 Oct;141(22):1647–9.
101. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001 May 31;344(22):1651-1658.
102. Dandona P, Karne R, Ghanim H, Hamouda W, Aljada A, Magsino CH. Carvedilol inhibits reactive oxygen species generation by leukocytes and oxidative damage to amino acids. Circulation 2000 Jan 18;101(2):122-124.
103. Packer M. β-Adrenergic blockade in chronic heart failure: principles, progress, and practice. Prog Cardiovasc Dis 1998 Jul 1;41(1):39-52.
104. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res 1997 Jul 1;35(1):30-34.
Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. Circ Res 1997 Jul 1;114(11):1788-1803.
105. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999 Sep 2;341(10):709-717.
Ussher JR, Campbell JE. Incretin-based therapies for the failing heart. Cardiovasc Endocrinol 1999 Sep 2;5(3):86-92.
106. Uribarri J, Oh MS, Carroll HJ. Hyperkalemia in diabetes mellitus. J Diabet Complicat 1990 Jan 1;4(1):3-7.
Halbirk M, Nørrelund H, Møller N, et al. Cardiovascular and metabolic effects of 48-h glucagon-like peptide-1 infusion in compensated chronic patients with heart failure. Am J Phys Heart Circ Phys 1990 Jan 1;298(3):H1096-H1102.
107. Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation 2004;109:962-965.
108. McMurray J, Ponikowksi P, Bolli GB, et al. The vildagliptin in ventricular dysfunction diabetes trial (VIVIDD). Eur J Heart Fail 2013 May 26;12:1. (Suppl).
112. Wang XF, Zhang JY, Li L, Zhao XY, Tao HL, Zhang L. Metformin improves cardiac function in rats via activation of AMP-activated protein kinase. Clin Exp Pharmacol Physiol 2011 Feb 1;38(2):94-101.
113. Kinsara AJ, Ismail YM. Metformin in heart failure patients. Indian Heart J 2018;70:175-176.
114. Eriksson L, Nystrom T. Activation of AMP-activated protein kinase by metformin protects human coronary artery endothelial cells against diabetic lipoapoptosis. Cardiovasc Diabetol 2014;13:152 https://doi.org/10.1186/s12933-014-0152-5.
115. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002 Aug 6;106(6):679-684.
116. Lavie CJ, Sharma A, Alpert MA, et al. Update on obesity and obesity paradox in heart failure. Prog Cardiovasc Dis 2016 Jan 1;58(4):393-400.
117. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003 Dec 9;108(23):2941-2948.
118. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med 2012;157:601-610.
119. Roumie CL, Min JY, McGowan LD, et al. Comparative safety of sulfonylurea and metformin monotherapy on the risk of heart failure: a cohort study. J Am Heart Assoc 2017 Apr 1;6(4), e005379.
120. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015 Nov 26;373(22):2117-2128.
121. Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013 Jul 11;369(2):145-154.