Current Medicinal Chemistry, 2018, *25*, 1510-1524

REVIEW ARTICLE

Clinical Approach to Diabetic Cardiomyopathy: A Review of Human Studies

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ARTICLE HISTORY

Received: August 12, 2016
Revised: March 15, 2017
Accepted: March 21, 2017

DOI:
10.2174/0929867324666170705111356

Abstract: ***Background*:** Diabetic Cardiomyopathy (DC) has been defined as a distinct entity characterized by the presence of diastolic or systolic cardiac dysfunction in a diabetic patient in the absence of other causes for Cardiomyopathy, such as coronary artery disease (CAD), hypertension (HTN), or valvular heart disease. Diabetes affects every organ in the body and cardiovascular disease accounts for two-thirds of the mortality in the diabetic population. Diabetes-related heart disease occurs in the form of coronary artery disease (CAD), cardiac autonomic neuropathy or DC. The prevalence of cardiac failure is high in the diabetic population and DC is a common, but underestimated cause of heart failure in diabetes. The strong association between diabetes and heart failure has fueled intense human and animal research aimed at identifying the mechanisms underlying diabetic myocardial disease. Despite significant progress made, the precise pathogenesis of diabetic Cardiomyopathy is yet to be clearly defined. Hyperglycemia, dyslipidemia and inflammation are thought to play key roles in the generation of reactive oxygen or nitrogen species which are in turn involved.

***Methods*:** We have reviewed the up-to-date scientific literature addressing these issues.

***Results*:** The myocardial interstitium undergoes alterations resulting in abnormal contractile function noted in DC. In the early stages of the disease, diastolic dysfunction is the only abnormality, but systolic dysfunction supervenes in the later stages with impaired left ventricular ejection fraction. Transmitral Doppler echocardiography is usually used to assess diastolic dysfunction, but tissue Doppler Imaging and Cardiac Magnetic Resonance Imaging are being increasingly used for early detection of DC. Diabetic patients with microvascular complications show the strongest association between diabetes and Cardiomyopathy, an association that parallels the duration and severity of hyperglycemia.

***Conclusion*:** The management of DC involves improvement in lifestyle, control of glucose and lipid abnormalities, together with treatment of hypertension and CAD, if present.

Keywords: Cardiomyopathy, diabetes, glucose dysregulation, heart failure, medication.

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1875-533X/18 $58.00+.00

1. INTRODUCTION

Worldwide, diabetes mellitus is now viewed as an epidemic, with cardiovascular disease being the primary driver of the raised levels of morbidity and mortality in diabetic patients. Besides an increased risk of cardiovascular disease in type 1 and type 2 diabetes (T2DM) mellitus, this risk may also be evident in pre-diabetic stages, driven by symptomatology such as impairments in fasting glucose and glucose tolerance, as well as wider processes associated with metabolic syndrome and obesity.

Diabetic patients have a high prevalence of heart failure or impaired diastolic and systolic cardiac function subsequent to hypertension, coronary artery disease and DC [1]. Diabetic patients have a two-fold increase in short- term mortality rate following acute myocardial infarction, compared to non-diabetic patients, with the glucose admission profile being a better predictor of outcome than glycated hemoglobin (HbA1c) after a heart attack in diabetic patients [2]. Consequently, the management of cardiovascular risk factors in T2DM is of great clinical importance, with wider implications driven by the financial and therapeutic/side effect burden of pharmaceutical treatment [3].

This review focuses on human studies, including pathophysiology, diagnostic evaluation and management options, whilst highlighting the clinical importance of early DC identification for the optimization of treatment in diabetic patients.

2. DEFINITION

The term DC was first introduced over 30 years ago, following evidence indicating that diabetes is associated with a distinct cardiomyopathy, which was independent of other known risk factors, such as hypertension and coronary artery disease.

Studies using cardiac catheterisation or echocardiography show diastolic dysfunction to be an early indicant of diabetes-driven heart muscle disease, with this preceding systolic dysregulation and associated damage. Many of the pathogenetic mechanisms underpinning the risk of DC have been identified, although in many cases, their mode of action has still to be clarified [4]. Metabolic abnormalities such as hyperglycemia, hyperinsulinemia and hyperlipemia may, both directly or indirectly, drive the alterations in cardiomyocytes that underpin DC pathophysiology, including myocardial fibrosis and myocardial hypertrophy.

Clinically, metabolic abnormalities are the main treatment target. Given that DC is also highly associated with asymptomatic T2DM patients, it is important that screening occurs early, in order to prevent the progression to chronic heart failure [5].

3. EPIDEMIOLOGY

Besides clinical studies, epidemiological data show a significant association of T2DM and heart failure. In diabetic and non-diabetic patients with symptomatic chronic heart failure, HbA1c levels are an independent risk factor for cardiovascular-associated death, and overall mortality as well as heart failure linked hospitalization [6]. A role for HbA1c levels was also indicated in a recent study of 20,985 T1DM patients [7]. These authors showed 3% of T1DM patients to be diagnosed with heart failure over a 9 yrs follow-up, giving an incidence of 3.38 events per 1,000 patient/year. The hazard ratio for the development of heart failure was four-fold higher when HbA1c levels >10.5%, *versus* controls with HbA1c <6.5% [7].

Hyperglycemia is associated with a change in glucose metabolism, leading to heightened beta-oxidation and consequent free fatty acid (FFA) damage, namely lipotoxicity, also in the myocardium. Hyperglycemia also associates with insulin resistance, activation of the renin-angiotensin-aldosterone system, changes in calcium homeostasis and structural changes in the natural collagen network. The latter can lead to a less flexible matrix, due to advanced glycation end-product (AGE) formation, hypertrophy and fibrosis, which all contribute to the pathophysiology of clinical DC phenotypes. Cardiac metabolism is significantly altered in diabetes, as indicated by reduced glucose utilization, lower rates of lactate oxidation and heightened use of fatty acids. Amino acid disturbances are also of potential clinical relevance due to quantitative and qualitative changes in contractile proteins [8].

4. STRUCTURAL/FUNCTIONAL CHANGES IN THE DIABETIC HEART

Significant alterations in the anatomy and the function of the myocardium underpin the clinico-pathological consequences of DC.

Myocardial structure is primarily comprised of small cardiomyocytes that are densely packed with mitochondria. The classical phenotype in DC is characterized by large areas of fibrosis and a marked reduction in sarcomeres. This contrasts to the pathophysiology typical of restrictive Cardiomyopathy, where the myocardial structure appears to be characterized by hypertrophic cardiomyocytes, collagen deposition between cardiomyocytes as well as preserved sarcomeres [9]. In

the early stages of DC, pathological alterations occur mainly at the level of myocardial interstitium (formation of AGEs, impaired compliance and ischemia of the vasa vasorum), with myocardial contractile dysfunction emerging as a consequence of such changes [10]. Later abnormalities, including ventricular myocardial hypertrophy, fibrosis (interstitial and perivascular) and cardiac microvascular abnormalities emerge.

4.1. Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) significantly predicts heart failure development, and associated mortality [11]. Hypertension is the main risk factor for LVH, although diabetes can also drive such pathological remodeling. Echocardiographic studies performed in diabetic patients have consistently shown a strong association between diabetes, increased LV mass, and LVH even in the absence of coexistent hypertension [12, 13]. Moreover, obesity itself also portends a raised risk of concentric LVH, which is independent of elevated blood pressure [14]. Although the precise mechanisms of the hypertrophic response to metabolic stress remain to be fully elucidated, LVH has become a defined structural characteristic of DC.

4.2. Diastolic Dysfunction

DC associated ventricular hypertrophy and fibrosis are the primary mediators of diastolic dysfunction.

Similar to the data on LVH in metabolic disease, diabetes is also strongly associated with diastolic dysfunction. In fact, diastolic abnormalities are thought to be among the earliest functional manifestations of DC. The prevalence of diastolic dysfunction in diabetics ranges between 40- 75% [15]. The mechanism of diastolic dysfunction in the diabetic heart may be a consequence of alterations in calcium handling, impaired energetics, cardiac lipid accumulation, and/or myocardial fibrosis. Interestingly, the early stages of diastolic dysfunction are reversible in diabetics who lose weight and normalize their metabolism [16]. This finding implies that the pathogenesis of DC may have a reversible phase and emphasizes the importance of early, aggressive lifestyle modification in diabetics with impaired myocardial relaxation.

4.3. Systolic Dysfunction

Systolic dysfunction is only evident at later DC stages. It is unknown whether systolic heart failure is the final common pathway of DC or is an alternate phenotype determined by the interaction of genetics and diabetes in susceptible individuals. It is also important to recognize that many diabetics with "normal" ejection fraction may actually have impaired systolic function when more sophisticated measures, such as myocardial strain measurements or tissue doppler, are employed [17]. To date, the early stages of systolic dysfunction are likely to go unrecognized clinically.

Cardiac output diminishes progressively with systolic dysfunction and disease severity. LV systolic ejection fraction is a reliable indicant of systolic dysfunction severity and associated heart failure.

5. FROM THE PATHOGENESIS TO A POSSIBLE THERAPY

DC pathogenesis is complex, typically showing changes in lipid metabolism, insulin resistance and mitochondrial function as well as alterations in adipokine secretion and signaling. Such factors suggest therapeutic approaches in DC (Table **1**) [18]. In summary, the most important aspects of DC include: 1) metabolic disturbances (insulin resistance, loss of glucose transporter 4, carnitine deficiency, alterations in calcium homeostasis and AGE); 2) myocardial fibrosis (in conjunction with heightened levels of angiotensin II, IGF-I, pro-inflammatory cytokines, and apoptosis); 3) microangiopathy (impaired coronary flow reserve, and endothelial cell function); 4) cardiac autonomic neuropathy (including denervation as well as changes in myocardial catecholamine levels); and 5) mitochondrial dysfunction**.** Each of these alterations suggests a possible therapy, as summarized in Fig. (**1**). In Fig. (**2**) we summarize the difference between the classical and other, different phenotypes, in particular, the relative importance of DM- related pathophysiological mechanisms for development of DC.

Table 1. Relationship between pathogenic mechanisms and possible specific therapeutic strategies.

Pathogenic Mechanisms	Possible Therapy
Metabolic disturbances	Lifestyle modification, hypoglycemic drugs and lipid-lowering therapy
Myocardial fibrosis	ACE inhibitors Angiotensin II receptor antagonists beta adrenoreceptor antagonists endothelin-1 receptor antagonists antioxidants (magniferin, metallothionein, vitamins C and E)
Microangiopathy	PKC-beta isoform inhibitor

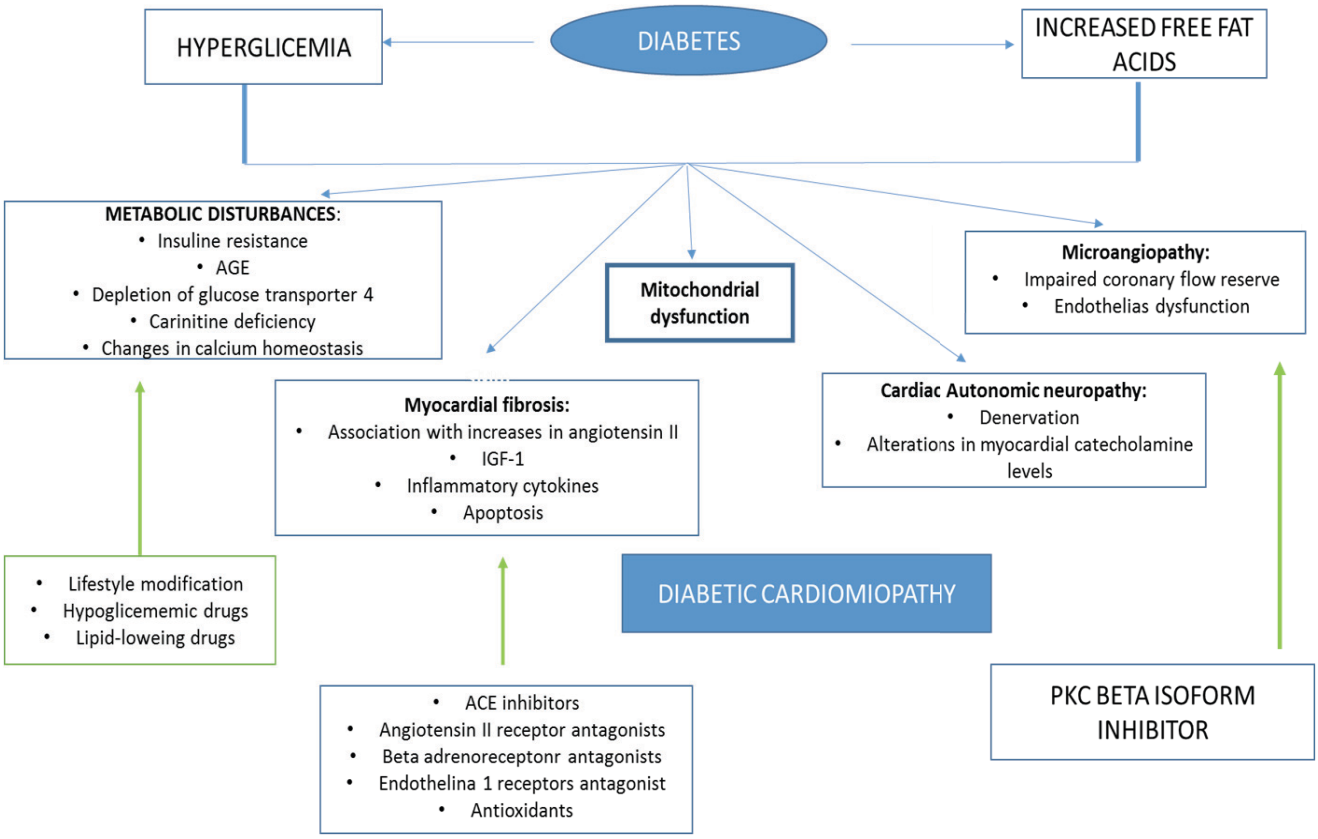

Fig. (1). Summary of the pathogenic mechanisms of diabetic Cardiomyopathy.

	DMCMP with restrictive/HFPEF phenotype	DMCMP with dilated/HFREF phenotype
Hyperglycaemia	+++	+
Lipotoxicity	+++	+
AGEs deposition	+++	+++
Microvascular rarefaction	+++	+++
Autoimmunity	–	+++
Insulin resistance/ Hyperinsulinaemia	+++	–

Fig. (2). A two-faced disease: restrictive or dilated phenotype diabetic Cardiomyopathy
HFPEF: Heart failure with preserved Ejection Fraction;
HFREF: Heart failure with reduced Ejection Fraction
(modified from Petar M. Seferović. *Eur. Heart J.,* **2015**).

5.1. Metabolic Disturbances

The effects of elevated glucose or altered insulin sensitivity on cellular components within the heart has significant impacts on cardiac extracellular matrix (ECM), contributing to the impact of diabetes in reducing cardiac function [19]. Factors contributing to such alterations in the ECM may include the heightened production, lower degradation and chemical modification of ECM proteins. The direct or indirect effects of high glucose concentrations may be driving such changes [20]. In particular high glucose concentration levels accelerate collagen types I and III synthesis, which an increase in extracellular signal-related kinase (ERK)1/2 signalling in cardiac fibroblasts may have an important role [21]. Moreover in diabetes, energy production shifts from glucose utilization to the beta-oxidation of FFA, which are supplied to cardiac cells from two sources, namely endogenously from the lipolysis of cardiac triglyceride stores, or exogenously from the blood.

In a state of impaired /deficient insulin secretion, adipose tissue lipolysis is increased, leading to a heightened level of circulating FFA. Also, hydrolysis of the augmented myocardial triglyceride stores may enhance tissue FFA. Regardless of the FFA source, their increased utilization can have negative impacts on myocardial function, including from the higher oxygen requirement required during FFA metabolism, potentially toxic FFA intermediate accumulation intracellularly, and a FFA- driven inhibition of the oxidation of glucose oxidation, as well as significant morphological changes. Therapies targeting such cardiac metabolic alterations in the early stages of diabetes would then

have the potential to delay the onset of more permanent sequelae [22]. The exposure to high levels of circulating FFA has been proposed to be a major contributor to DC [23]. Data in women classed as overweight or obese, indicate insulin resistance to be linked to heightened myocardial triglyceride content and cardiac remodelling as well as lower diastolic function [24].

High density lipoprotein (HDL) cholesterol may indirectly modulate DC, *via* the regulation of metabolic triggers, such as hyperglycemia, hyperinsulinemia, and hyperlipidemia. Such factors can drive DC associated cellular changes by a variety of processes, as detailed above, including immune-inflammatory processes, and Ca^{2+} handling, as well as oxidative and nitrosative stress, and endothelial dysregulation [25]. Disturbed glucose metabolism can lead to AGE formation, which can associate with lipofuscin, and is linked premature cell ageing. A recent investigation assessed heart failure and AGE formation in patients with or without T2DM. The amount of AGE in cardiomyocytes increases significantly, both in diabetes and heart failure, with a staining pattern that is typical for each condition [26]. As previously indicated oxidative stress has a significant impact on the pathogenesis of DC, suggesting the potential utility of antioxidant therapy [27]. The inflammation associated transcription factor, nuclear factor-kappa B (NF-kB), is an important driver of many of the changes occurring across an array of medical conditions, including different heart diseases. As such, NF-kB may be a crucial driver of many of the processes linked to DC, including oxidative stress and inflammation [28]. The post-translation attachment of O -linked N-acetylglucosamine, or O-GlcNAc, to serine and threonine residues within both nuclear and cytoplasmic proteins, is achieving growing recognition as an important regulator of an array of cellular processes. The heightened and sustained enhancement of O-GlcNAc levels are associated with glucose toxicity and insulin resistance. Increased O-GlcNAc levels could contribute to the negative impacts of diabetes on the heart, including impairments in contractility and calcium handling, as well as stress responses. As recent data indicates that O-GlcNAc modulates epigenetic processes, this could be another ubiquitious mechanism that may contribute to diabetes-driven changes in DC [29].

No single pharmaceutical can treat DC, with management thought to necessitate a variety of approaches, including: lifestyle modification; glucose control (insulin, sulfonylureas, thiazolidinediones, alpha glucosidase inhibitors, biguanides, meglitinides and dipeptidyl peptidase 4 (DPP-4) inhibitors); GLP -1 analogs; calcium channel blockers (amlodipine, verapamil); ACE inhibitors (captopril, enalapril); angiotensin II receptor antagonists (losartan, olmesartan); endothelin-1 receptor antagonists (bosentan, tezosentan); beta adrenoreceptor antagonists (acebutolol, carvedilol); peptides (adrenomedullin); antioxidants (methalothionein, alpha tocopherol, alpha lipoic acid); and antihyperlipidemic drugs (fenofibrate, simvastatin, ezetimibe [30].

5.2. Microangiopathy

Hemodynamic and structural changes, such as capillary basement membrane thickening, and interstitial fibrosis as well as myocyte hypertrophy and cellular necrosis can arise as a result of changes in several factors including vasoactive molecules, which may be crucial in mediating the deficits in structure and function during the early and late disease stages [31]. Moreover, diabetes affects the heart *via* a quantifiable increase in chamber visco-elasticity rather than an increase in chamber stiffness and the phenotypic characterization of DC is facilitated by diastolic function assessment [32]. A new role of DPP4 in micro- and macro-vascular vessels is emerging [33, 34].

Diastolic dysfunction and microvascular function may be intimately linked, although the relationship between endothelial dysfunction, profibrotic connective tissue growth factor and refined measures of diastolic dysfunction is not strong, suggesting that other factors may be crucial to the early pathogenesis of subclinical cardiac diastolic dysfunction common in T2DM [35]. Diabetic patients with microangiopathy have impairments in left ventricle functioning, whereas those with uncomplicated diabetes have normal function. This suggests the existence of a specific subtype of DC with microangiopathy, but not with a metabolic defect. The linking of microangiopathy and suboptimal left ventricle functioning may underpin the high immediate mortality and the heightened incidence of cardiogenic shock and congestive heart failure that is evident after myocardial infarction in diabetic patients [36]. Although requiring further investigation, such studies may suggest a subclinical DC that arises from small-vessel disease [37].

Human diabetes mellitus shows evidence of decreased cardiac myofilament functioning, which, coupled to depressed cardiac myofilament Ca^{2+} responsiveness, may underpin the suboptimal ventricle functioning that is characteristic of DC [38]. Recent data indicates that diabetes depresses AMP-activated protein kinase (AMPK) activity, thereby promoting the

interaction of BECN1 and the anti-apoptotic protein, BCL2. Concurrently, diabetes increases the risk of cardiomyocyte apoptosis, whilst also suppressing cardiac autophagy. AMPK activation leads to MAPK8 phosphorylation, in turn driving BCL2 phosphorylation and is dissociation from the BECN1-BCL2 complex. Therefore AMPK, *via* BCL2, restores cardiac autophagy, protects against cardiac apoptotic processes, thereby better optimizing cardiac structure and function.

The dissociation of BCL2 from BECN1 through the activation of MAPK8- BCL2 signalling may be important in driving the processes through which AMPK activation can restore autophagy, whilst protecting against cardiac apoptosis and preventing DC [39].

Protein kinase C (PKC) is linked to alterations in the vasculature, including increasing permeability, extracellular matrix synthesis, contractility, cell growth, apoptosis, angiogenesis and leukocyte adhesion, as well as both cytokine activation and inhibition. Different PKC isoforms (PKC-alpha, -beta1/2, and PKC-delta) underpin such perturbations in vascular cell homeostasis, including in large as well as small vessels. In clinical trials, a PKC-beta isoform inhibitor has shown positive effects in diabetic non proliferative retinopathy and nephropathy, as well as in endothelial dysfunction [40]. The selective inhibition of PKC βII represents an effective approach for treating microvascular complications [41].

5.3. Myocardial Fibrosis

A number of factors contribute to the dysregulation of cardiac insulin and metabolic dysregulation, including: systemic insulin resistance, adipokine secretion dysregulation, hyperinsulinemia, raised levels of circulating inflammatory mediators, aberrant renin angiotensin aldosterone system activation and increased oxidative stress, which all contribute to diastolic dysfunction. Suboptimal calcium homeostasis and endothelial cell dysregulation as well as endoplasmic reticular stress may also contribute to cardiomyocyte fibrosis and diastolic dysfunction [42]. Many investigators have proposed that inhibiting the renin-angiotensin-aldosterone and sympathetic nervous systems may have clinical utility in DC patients. The efficacy of angiotensin II and aldosterone blockade has been proposed to be mediated, at least in part, by aldosterone blockade leading to the down-regulation of the activity of the Na(+)/H(+) exchanger 1. Such a role for the regulation of ion channels in DC requires further investigation [43]. Apoptosis is crucial to the pathophysiology of most medical conditions, including DC, by driving the death of terminally differentiated cardiomyocytes. The efficacy of apoptosis inhibition in preventing the development of heart failure has been shown in many studies. We now review the role of apoptosis across cardiovascular diseases, especially its role in the molecular processes driving cardiomyocyte death [44].

The FKHR gene product, FoxO1, belongs to the forkhead box family of transcription factors, and contributes to the regulating of metabolism, cell proliferation, the oxidative stress response and immune homeostasis as well as having a role in cell death processes. Given that FoxO1 has cardio-protective effects against an array of stressors, it has been the subject of investigation in regard to DC. The cardiac tissue- specific deletion of FoxO1 affords protection to the heart against Cardiomyopathy, whilst FoxO1 down-regulation in endothelial cells may afford protection against atherosclerotic plaques [45]. Future studies will have to clarify the role of FoxO1 in the etiology, course and management of DC. Two important pathways are involved in development of cardiac fibrosis: the renin-angiotensin system and AGE and its receptor, RAGE. Cardiac fibrosis is an important component of DC, with a recent study suggesting a possible crosstalk between the RAS and AGE/RAGE pathway in the etiology of cardiac fibrosis in diabetes [46]. There is a growing appreciation of the multitude of roles and impacts of the renin-angiotensin-aldosterone system, including in the regulation of diabetes [47]. Other processes may also be relevant, with data indicating that endothelin-1 and Na + /H + exchanger -1 (NHE-1) can lead to cardiomyocyte hypertrophy *via* the activation of the MAPK activation pathways, suggesting a role in DC [48]. More recently, it has been shown that the role of AMPK extends to several non-metabolic effects related to other cardiac diseases, suggesting that AMPK could play both physiological and pathophysiological roles in the regulation of cardiac metabolism and wider heart functioning [49]. Matricellular proteins are induced following cardiac injury and the process of cardiac remodeling heart, where they act to regulate inflammatory, reparative, fibrotic and angiogenic processes. Thrombospondin (TSP)-1, -2, and -4, tenascin-C and -X secreted protein acidic and rich in cysteine (SPARC), periostin, osteopontin, and the CCN family members, such as CCN1 and CCN2/connective tissue growth factor, are important regulators of an array of cardiac conditions and pathophysiological processes, including DC [50]. Both ramipril and telmisartan, used in the treatment of hypertension, improve echocardiographic left ventricular diastolic indices, whilst lowering plasma brain natriuretic peptide (BNP) levels in patients with

diabetes, especially when used in combination [51]. An array of other medications and factors show evidence of decreasing interstitial fibrosis and improving heart functioning in DC, including beta- adrenoreceptor antagonists, ACE inhibitors, Bonestan, an antagonist at the endothelin-receptor antagonist, and adrenomedullin, as well as hormones, such as (insulin, IGF-1, and antioxidants, including vitamins C and E, magniferin and metallothionein [52]. Clinical trials are necessary to clarify the utility of such data [53]. Other data has implicated a role for immune cells in DC, with myeloid dendritic cells being upregulated in the course of insulin-resistance and obesity, which may modulate the pathological vascular remodeling evident in DC [54].

5.4. Cardiac Autonomic Neuropathy

Autonomic dysfunction, in the form of cardiovascular autonomic neuropathy, is not uncommon in diabetes mellitus and is proposed to be associated with heart rate control dysregulation as well as abnormalities in vascular dynamics. Moreover, cardiac autonomic neuropathy is linked to left ventricular diastolic dysfunction (LVDD) in T2DM patients with no clinical manifestations of heart disease. DC can be detected by 24hr ECG monitoring and echocardiography, including in the early stages of DC and is recommended as an assessment in all patients at risk [55]. The diastolic dysfunction of T2DM associates with sympathetic integrity regional markers as well as autonomic neuropathy clinical markers [56].

LVDD and cardiac autonomic neuropathy (CAN) may be present in otherwise well-managed T2DM patients. The parameters defining LVDD and CAN may useful in better identifying DC, and therefore could prove to be good prognostic indicators, as in nondiabetic populations [57].

5.5. Mitochondrial Dysfunction

Evidence indicates that myocardial metabolism is significantly changed in diabetes, which is thought to contribute to contractile dysfunction as well as ventricular failure. Mitochondria are crucial to alterations in metabolism, and have a role in DC recent data [58].

Cardiomyocytes are packed with mitochondria, so any progressive decline in mitochondrial functioning will contribute to heart senescence. Suboptimal mitochondrial functioning leads to lower levels of ATP production and higher levels of ROS, with both changes contributing to an increased likelihood of apoptosis. Dysfunctional mitochondria also need to be removed in order to optimize cell functioning, which is achieved by macroautophagy, a process that is less efficient with advancing age. As such, the activity, movement and disposal of mitochondria are important in heart senescence as well as age-related cardiovascular diseases more widely.

Interventions that inhibit cardiac ageing, will lead to improvements in mitochondria functioning as well as macroautophagy and the oxidative/antioxidative balance, suggesting impacts on key processes of cellular functioning and important therapeutic targets in DC [59].

5.6. Other Possible Future Therapy

Zinc homeostasis is as a growing area of research in cardiovascular disorders. Zinc is important in the maintenance of cellular structure and physiology. As such, zinc replenishment can improve cardiac function as well as prevent any further damage [60].

Another candidate is represented by cardiac ryanodine receptors (RyR2s) that act on the redox regulation of the cardiac Ca(2+) transport systems and could have a role in redox regulation of pathological cardiac dysregulation that is present in diabetes [61].

Diabetes associated cardiac fibrosis is linked to the endothelial-to-mesenchymal transition process, which is positively modulated by endothelin 1 (ET-1). This suggests that the targeting ET-1 from endothelial cells may have treatment efficacy in DC [62].

Hyperglycemia can contribute to raising levels of the pro-inflammatory cytokine, macrophage migration inhibitory factor (MIF), which increases the likelihood of developing Cardiomyopathy in T2DM patients, with increased levels of MIF also contributing to wider symptomatology. The elevated levels of cardiac dysfunction in T2DM patients [63]. The identification of the mechanism underlying such hyperglycemic-driven effects should aid in the search for new treatment targets in DC [64].

In addition to life style modifications, and well researched treatments, such as ACE inhibitors, beta-blockers and angiotensin II receptor antagonists, trimetazidine may be usefully administered to patients showing impaired glucose tolerance and/or in the early course of T2DM. This is proposed, given that trimetazidine can act as a metabolic switch, leading to the preferential use of glucose over FFA as the metabolic substrate in cardiomyocytes [65]. Trimetazidine may also lower the prevalence of heart failure as increase long-term survival in T2DM patients, in part *via* the early normalization of the substrate of myocardial metabo-

lism [66]. Further investigation on the potential efficacy of trimetazidine on idiopathic dilated Cardiomyopathy in diabetic patients is required.

Galanin can modulate glucose homeostasis and carbohydrate metabolism in cardiomyocytes as well as in skeletal muscles. Galanin also increases the expression levels and translocation of the glucose transporter 4 (GLUT4) in insulin-sensitive cells, thereby lowering levels of insulin resistance. Such data suggests that endogenous galanin is likely to positively regulate the diabetic heart [67].

A recent study in a DC model, investigated the cardio-reparative properties of sildenafil, which is well researched selective phosphodiesterase type 5 inhibitor. Given that an early aspects of DC include LV concentric hypertrophy in association with alterations in the dynamics of myocardial contraction, it is of note that the chronic inhibition of phosphodiesterase type 5, at such an early stage, inhhibits remodelling, with consequent benefits in icardiac kinetics as well as circulating markers. This effect seems to be mediated *via* direct impacts on intramyocardial activity, being independent of vasodilatory and endothelial cell regulation [68].

A growing body of data indicates a role for the fatty acid transporter and scavenger receptor, CD36, in the etiology of insulin resistance and the development of T2DM associated cardiovascular problems. The shift of CD36 to the plasma membrane from intracellular stores occurs early in the heart during the course of diet induced obesity and the development of insulin resistance. This CD36 shift increases the rate of fatty acid uptake, leading to fatty acid incorporation into triacylglycerol stores and consequently to lipid intermediates, with these changes compromising insulin-induced GLUT4 recruitment. Such data indicates that CD36 requires further investigation, including as a therapeutic target in the redirecting of body fatty acid fluxes [69].

6. DIAGNOSIS

Most DC cases may be subclinical, with no evident overt symptoms, such as changes in left ventricular mass, wall thickness and cardiac cavity dimensions. However, Cardiomyopathy-related abnormalities are functionally expressed and can be detected by echocardiography.

The initial DC stages show a deterioration in longitudinal systolic function that is compensated by an elevation in the radial function. Diastolic dysfunction is also an initial sign. A shift from functional to morphological changes occurs as DC progresses, including left ventricular concentric hypertrophy and fibrosis, as indicated above. End stage DC characteristics include a reduction in the ejection fraction as well as ventricular dilatation, whilst the very late stages can often mimic dilatative Cardiomyopathy [70]. The analysis of diabetic heart disease with pulsed Doppler techniques in order to assess the systolic and diastolic functioning of the left ventricle, is important to investigate in all indicated patients, as an asymptomatic patient can show indications of diastolic dysfunction that is treatable [71]. Early stage DC can also be indicated by Doppler imaging, which is clinically important at an early stage where left ventricular diastolic dysfunction, without any obvious clinical symptomatology [72]. As indicated above, diabetes leads to myocardial damage leading to diastolic dysfunction, prior to any systolic dysfunction.

Diastolic dysfunction significantly correlates with disease duration, as well as glycemic levels and the patients treatment history. Echocardiography is a relatively inexpensive investigative tool that detects structural and functional cardiac abnormalities. It should also be noted that systolic dysfunction can be detected by the standard echocardiography in the relatively early stages.

Transmitral Doppler (Mitral valve blood flow measured by pulsed wave Doppler) is the standard procedure for the assessment of ventricular diastolic function [73]. Transmitral Doppler measures a number of variables, including: the early (E-wave) and late (A-wave) ventricular filling waves, providing an E/A ratio; the isovolumetric relaxation time (IVRT); the E-wave deceleration time (EDT); the E-wave peak velocity (E); and the A-wave duration (A-dur). Diastolic function, on the basis of such measures, can be categorized accordingly: (1) normal pattern; (2) grade I (impaired relaxation); (3) grade II (pseudonormal pattern); and (4) grade III (restrictive pattern) [74]. Grade I diastolic dysfunction patients show an E/A ratio < 1, arising from a lower early and raised late diastolic flows [75]. This assessment is routinely administered to diabetic patients, prior to the reporting of any cardiac symptoms [76].

Some authors have suggested that plasma BNP may be utilized as an alternative screening tool for the identification of subclinical LV dysfunction. However, other alternative screening approaches, such as BNP, are not sufficiently sensitive in the case of subclinical dysfunction presentations [77]. Modern tissue Doppler applications have greater sensitivity for diagnosing dia-

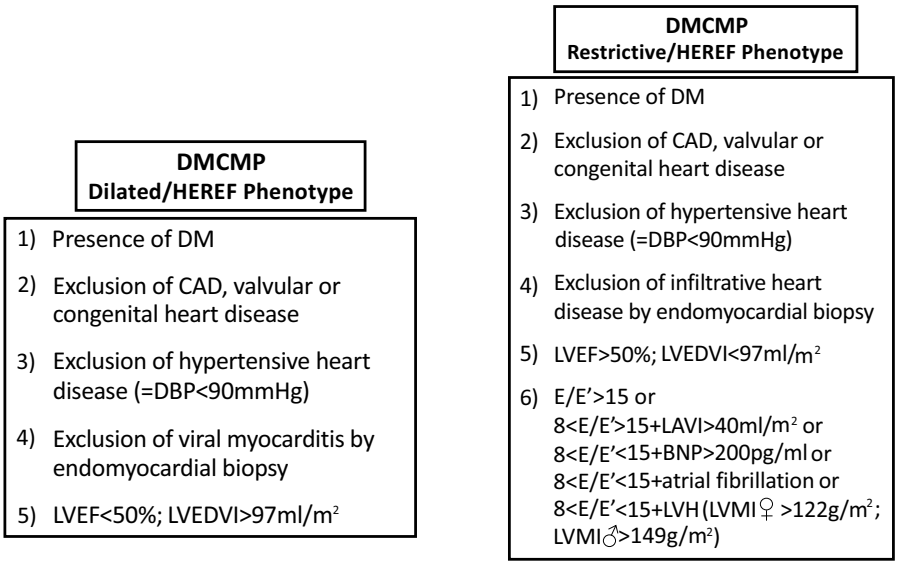

Fig. (3). Possible diagnostic criteria for the two subtypes of diabetic Cardiomyopathy (modified from Petar M. Seferović. Eur Heart J 2015).

stolic dysfunction, when compared to pulsed Doppler (63% *vs.* 50%) [78] and they may detect abnormalities of diastolic function when the patient is still asymptomatic and their systolic function is normal. Tissue Doppler imaging (TDI) measures myocardial tissue velocities over the cardiac cycle, allowing the quantitative assessment of myocardial global and regional systolic and diastolic functions [79, 80]. TDI allows myocardial tissue velocities measurement in the longitudinal direction, as well as peak early diastolic myocardial velocity (E0), which is a reflection of global left ventricular diastolic function [81].

As well as such conventional assessment tools, newer approaches to the diagnostic measurement of myocardial fibrosis and cardiac metabolic dysfunction include magnetic resonance imaging (MRI) and spectroscopy plus contrast agents. When complemented with serum biomarkers such strategies provide a valuable indication of diabetes-driven alterations in cardiac structure and function, including the very early stages of disease manifestation [82]. Furthermore, MRI is gaining popularity as a valuable diagnostic tool for myocardial disorders [83, 84], including by demonstrating the presence of fatty or fibrosis infiltrates in the hypertrophied myocardium, as well as a notable alteration in the myocardial geometry and ventricular mass. Generally, left ventricular diastolic and systolic functional abnormalities have been detected in 21% and 15% of the asymptomatic diabetic patients, respectively [85]. Cardiac MRI also has utility in the detection of diastolic dysfunction and myocardial steatosis [86].

Cardiac MRI, using different radionuclides, and positron emission tomography (PET) clearly have utility in the diagnosis of DC. The cutting edge of diagnostic imaging in diabetes, includes: 1) PET, which can measure resting and stress blood flow as well as coronary flow reserve; 2) radionuclide procedures that measure aerobic and anaerobic cardiac metabolic activity; and 3) cardiac neurotransmission imaging, which is useful in the diagnosis and evaluation of autonomic neuropathy [87].

As indicated above, both metabolic and vascular disturbances contribute to DC. The correlation among myocardial diastolic dysfunction, metabolic disturbances, and post-contrast T1 values supports the role of diffuse myocardial fibrosis in the biological underpinnings of early DC [88]. Fig. (**3**) shows possible diagnostic criteria for the diagnosis of the two DC subtypes.

7. IS IT POSSIBLE TO PREVENT DC?

Some studies have proposed possible strategies for preventing DC, although we are far from being able to identify patients at risk of developing DC. Only study that has evaluated the DC predictors, showing that apolipoprotein 1 has predictive utility [87-89].

Cardiovascular complications are major contributors to the heightened mortality and morbidity levels in diabetic patients, with epigenetic changes, as a consequence of environmental factors and their interactions with genetic factors, proposed to play an important role in disease susceptibility. Epigenetic mechanisms, including DNA methylation, microRNA, chromatin remodelling and histone modifications are powerful regu-

lators of gene expression, with relevance to the pathophysiology of DC [90, 91]. MicroRNAs are a novel group of non-coding small RNAs that co-ordinate gene activity patterns, being increasingly recognized to have a significant role in a wide array of physiological and pathophysiological processes. Recent studies indicate that microRNAs have a critical role in cardiovascular complications, as well as having utility as blood biomarkers [92-94].

A recent study showed that lower eNOS expression can predispose to impaired glucose homeostasis, with consequences for cardiovascular diseases [95], whilst other researchers have suggested adipokines as potential novel predictors of cardiovascular diseases, and therefore with potential to treat prior to obvious symptomatology [96].

8. ORAL GLUCOSE-LOWERING THERAPIES: INFLUENCE IN CARDIOVASCULAR MORBIDITY AND MORTALITY

An important year for cardiac dysregulation in diabetes was 2013 for two reasons: 1) a major revision of the clinical guidelines for heart failure with comorbid diabetes was published [97]; and 2) there was an unexpected increase in heart failure incidence in the clinical trials of saxagliptin *versus* placebo [98]. A large scale clinical trial in 2008 suggested intensive glycemic control increased, rather than decreased, cardiovascular mortality in patients with diabetes [99]. In the same year, the Food and Drug Administration gave their approval of oral glucose-lowering therapies for T2DM, with an approval that was contingent on an effective reduction in HbA1c reduction followed by a postmarketing cardiovascular outcomes trial that had predefined end points, with relatively longer follow-up periods, and tested in a sample of patients at high risk, with efficacy criteria requiring a demonstration of "noninferiority" to placebo. Incretin-based therapies were the initial drugs evaluated under this new guidance policy [100]. The cardiovascular side effects of anti-diabetic drugs are believed to be an important reason for the increased heart failure risk in intensive glycemic control patients. Most of the currently available oral anti-diabetic drugs have more or less shown adverse cardiovascular side effects. In addition to DPP4 inhibitors, commonly used oral anti-diabetes agents, include biguanides, thiazolidinediones, and sulfonylureas [101], with the biguanide, Metformin, contraindicated in diabetic patients with heart failure, likely from an increased risk of lactic acidosis. However, later studies demonstrated that metformin is safe and may be linked to a lower morbidity and mortality in diabetic patients with established heart failure, when compared to other anti-diabetic therapy.

However, it should be noted that no placebo-controlled large scale trials on heart failure are available [102, 103], with the thiazolidinediones, such as rosiglitazone and pioglitazone, linked to increased heart failure and fluid retention [104]. Sulfonylureas seem to produce a dose-dependent and time-dependent increase in the risk of heart failure, whilst clinical evidence has shown the 2nd generation of sulphonylureas (glipizide, gliquidone, glimepiride, glibenclamide, and gliclazide) to have an increased the risk of developing congestive heart failure by 18%, compared to metfomin [105]. In another study following 4,902 diabetic women for a mean duration of 11 years, Li *et al*. reported that sulfonylurea increased the risks of coronary heart disease [106].

In contrast, preclinical data on GLP-1 agonists and DPP4 inhibitors, indicate that they promote nonglycemic-mediated cardioprotective effects. To date, 3 DPP4 inhibitors (saxagliptin [107], alogliptin [108], and sitagliptin [109] and one GLP-1 agonist (lixisenatide [110], published data on cardiovascular outcomes. Their results have questioned the cardiovascular safety, especially in regards to heart failure from the DPP4 inhibitors class, following the completion of two large clinical trials [106, 107]. While both trials showed no significant increase risk in composite cardiovascular outcome measures, the SAVOR-TIMI 53 trial reported a 27% rise in hospitalization for heart failure, but not in heart failure mortality.

There have been two other large scale trials, one on DPP4 inhibitor sitagliptin (TECOS) and one on GLP-1R agonist lixisenatide (ELIXA), which reported no excess heart failure risk. Future studies will be required to clarify the implications of these studies.

Studies in humans confirmed the vasodilatory effect of GLP-1. GLP-1 analogs are also able to reduce blood pressure by increasing urinary sodium excretion, promoting atrial natriuretic peptide (ANP) release from the atrium, and relaxing vascular smooth muscle cells. Activation of GLP-1R in the central nervous system induces satiety and thus reduces body weight and cardiovascular risk. In addition to enhancing GLP-1 effects, DPP4 inhibitors also increases stromal cell-derived factor (SDF)-1, a chemoattractant for many types of hematopoietic cells, including cardiac stem cells, endothelial progenitor cells, and mesenchymal stem cells.

Preservation of SDF-1 by DPP4 inhibition enhances chemotaxis and the repopulation ability of hema-

topoietic progenitor cells and stem cells, increasing the neovascularization of injured tissues [111]. A further prospective study on heart failure risk induced by anti-diabetic medications are under consideration for the incidence of hypoglycemia, heart failure, and cardiac function [112].

Empagliflozin iselectively inhibits the sodium-glucose cotransporter 2 (SGLT2), and is used in the management of T2DM. By inhibiting SGLT2, empagliflozin reduces the reabsorption of glucose in the kidney and therefore increases glucose excretion in the urine. As well as lowering hyperglycemia, empagliflozin is associated with a number of other changes, including osmotic diuresis, lower body weight and blood pressure without raised heart rate, whilst it also has favourable impacts on markers of arterial stiffness and vascular resistance and albuminuria, as well as serum uric acid [113]. In the EMPA-REG OUTCOME trial, empagliflozin lowered the primary composite outcome on cardiovascular death as well as lowering non-fatal myocardial infarction and non-fatal stroke, including lowering cardiovascular death by 38%, hospitalization for heart failure by 35%, and overall mortality by 32%, *versus* placebo, in T2DM patients with a high cardiovascular risk over a median time period of 2.6 years.

The effect of empagliflozin on heart failure hospitalization, cardiovascular death and on all-cause hospitalization was present early in the trial, being sustained throughout. This indicates a non-atherosclerosis related effect, with efficacy that requires clarification in future studies [114].

Recently, Ferranini [115] hypothesized that SGLT2 inhibitor-driven mild, persistent hyperketonemia, b-hydroxybutyrate is readily taken up by the heart, where it is oxidized in preference to fatty acids. Such an alteration in fuel selection improves the transduction of oxygen consumption and consequently mitochondrial functioning. In addition, the hemoconcentration following SGLT2 inhibition increases oxygen release to the tissues. These mechanisms may interact with the other SGLT2-induced changes, such as lowering blood pressure and increasing diuresis that would be expected to afford some cardioprotection, as indicated in the EMPA-REG OUTCOME trial.

Given the microvascular benefit of improved glycemic control, the identification of diabetic medication with a safe cardiovascular profile and which significantly lowers glucose is still an unfulfilled clinical need and target, requiring future investigation and long-term outcome studies [100].

CONCLUSION

These recent insights provide important additions to our knowledge regarding DC, although much remains to be discovered. In particular, specific pharmacotherapies for DC are required that reduce the raised levels of cardiovascular morbidity and mortality in diabetic patients. It is important to detect DC in the early stages as well as research of DC in asymptomatic diabetic patients, which may help to stop the progression to heart failure. It is clear that further work is required on the biochemical underpinnings in different cell types that produce a bias toward DC symptomatology, which may provide more targeted pharmaceutical treatments.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest with respect to the authorship and/or publication of this article.

ACKNOWLEDGEMENTS

Financial support: the study was supported by the "5x1000" voluntary contribution, by a grant (GM) through Division of Internal Medicine and Chronobiology Unit (RC1504ME53, RC1603ME43, RC1703 ME43), IRCCS Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", Opera di Padre Pio da Pietrelcina, San Giovanni Rotondo (FG), Italy.

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