



Global Advanced Research Journal of Medicine and Medical Sciences (ISSN: 2315-5159) Vol. 8(4) pp. 020-027, November, 2019
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Review

Diabetic Cardiomyopathy Pathophysiology and Update on Treatment

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Accepted 15 November, 2019

The presence of diabetes in HF patients portends worse prognosis than does HF without DM. Heart failure in diabetes mellitus (DM) in the absence of conventional risk factors such as hypertension, coronary artery disease (CAD), and congenital or valvular heart disease, has been defined in the literature as diabetic cardiomyopathy (DCM). The question what are the link between DM and DCM? The answer of this question is not well understood. This review will identify the link between diabetes mellitus and DCM, will also explore the possible mechanisms and triggering factors or associations with emphasis upon the implications of new anti-diabetic treatment on preventing development of heart failure in DM. The keywords used in the literature search were heart failure, diabetes mellitus, cardiovascular disease in DM, diabetic cardiomyopathy and treatment of diabetes with heart failure. These keywords were synced into midline and google search to acquire literature reviews and structured topics in order to deliver significant understanding of the mechanism and factors contributing to the development of DCM. All heart failure secondary to known etiology such as hypertension, valvular heart disease, coronary artery disease or cardio-myopathy without diabetes mellitus excluded. This literature review identify several link between diabetes mellitus and heart failure in the absence of conventional risk factors (DCM), it also explore the possible mechanisms and triggering factors or associations with emphasis upon the implications of new anti-diabetic treatment on preventing development of heart failure in diabetic patients. It also give conception on what remedy can change the course of this disease. DCM has a distinct substrate in DM patients with HF in the absence of known causes of heart diseases and its factors. All proven evidence-based medicine for its treatment should be taken into consideration. Uses of new anti-diabetic medication may delay or prevent development of DCM. Further clinical studies and basic science advancement will recognize the context of DCM.

Keywords: Diabetes mellitus, Diabetic cardiomyopathy, Heart failure

List of abbreviations

HF: Heart failure, **DM:** Diabetes mellitus, **DCM:** Diabetic cardiomyopathy, **CAN:** Coronary artery disease, **MI:** Myocardial infarction, **ICM:** Idiopathic cardio myopathy, **PKC:** Protein kinase C, **ROS:** Reactive oxygen species, **FA:** Fatty acid, **FFA:** Free fatty acid, **LV:** Left ventricular, **RAAS:** Renin Angiotensin Aldosterone System, **ACEI:** Angiotensin converting enzyme inhibitor, **ARBs:** Angiotensin receptor blockers, **BB:** Beta Blocker, **TZDs:** Thiazolidinediones, **DPP-4:** Dipeptidyl peptidase 4, **SGLT:** Sodium Glucose-Linked Transporter

BACKGROUND

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairments of ventricular filling or ejection of blood (Yancy et al., 2013). HF was associated with worse 5-year adjusted mortality than that of four common cancers, with the exception of lung cancer, in Scotland (Stewart et al., 2001). HF is

responsible for high morbidity and mortality: in-hospital mortality of HF varied from 2.4% in the TSOE-HFrEF Registry to 10.2% in a Canadian study (Wang et al., 2016; Adams et al., 2005; Harikrishnan et al., 2015; Tu et al., 2009). In type 2 diabetes mellitus (DM), 65% of death was due to cardiovascular disease. DM was responsible

Table 1. Staging of heart failure.

Stage	Descriptions
A	At high risk for HF but without structural heart disease or symptoms of HF.
B	Structural heart disease but without signs or symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.
D	Refractory HF requiring specialized interventions.

for a 2-5-fold increase in HF and a 2-4-fold greater stroke risk, compared with non-DM. Finally, risk of coronary artery disease (CAD) death was 2-4-fold higher in DM (Bell, 2003). HF survival was worse in the presence of diabetes: the 5-year survival was 46% in those with HF alone but only 37% for those with both diabetes and HF (From et al., 2006).

DM as a risk factor for cardiovascular disease is well defined and is considered as stage A HF, but DM as a direct cause of HF was not recognized until 1972. The term diabetic cardiomyopathy (DCM) was introduced by Ruble et al. in post-mortem studies in diabetic patients with HF in whom alcohol, hypertension, epicardial coronary disease and other structural heart disease had been ruled out as possible causes (Rubler et al., 1972). Since then, reports followed explaining the metabolic linkage between DM and HF. In diabetic patients, the prevalence of DCM was 12% and reached 22% in people over 64 years old (Bertoni et al., 2004).

Phenotypically, HF is broadly divided into diastolic and systolic HF. Reports indicate that diastolic HF is a primary presentation of heart disease that is often already present in young, apparently 'healthy' diabetic people without additional cardiovascular risk factors (Zonerach and Mollura, 1993). The diastolic dysfunction in DM patients was confirmed by autopsy studies that extensively summarized the morphological alterations that occur in the diabetic heart. The most consistent findings were myocyte hypertrophy, deposition of glycoproteins positive for periodic acid-Schiff (PAS) staining, interstitial edema, extracellular matrix accumulation and myocyte loss with subsequent replacement by interstitial connective tissue (Hardin, 1996; Shehadeh and Regan, 1995). In this review, we will address the mechanisms of the biochemical and clinical linkages between DM and DCM, in addition to the treatment of DCM.

METHODS

The factors and mechanisms of DCM has been detected as a major eye opener and should not be neglected. **We addressed the Question is diabetic cardiomyopathy standalone entity as a cause of heart failure?** The following keywords used in the literature search were heart failure, diabetes mellitus, and cardiovascular

disease in diabetic patient, diabetic cardiomyopathy and treatment of diabetes with heart failure. These keywords were synced into midline and google search to acquire literature reviews and structured topics in order to deliver significant understanding of the mechanism of diabetic cardiomyopathy. It will also lead to comprehension on which factors are contributing to the development of DCM and will give conception on what remedy can change the course of this disease. All heart failure secondary to known etiology such as hypertension, valvular heart disease, coronary artery disease or cardio-myopathy without diabetes mellitus excluded.

1 The evidence of DCM as stand-alone clinical entity

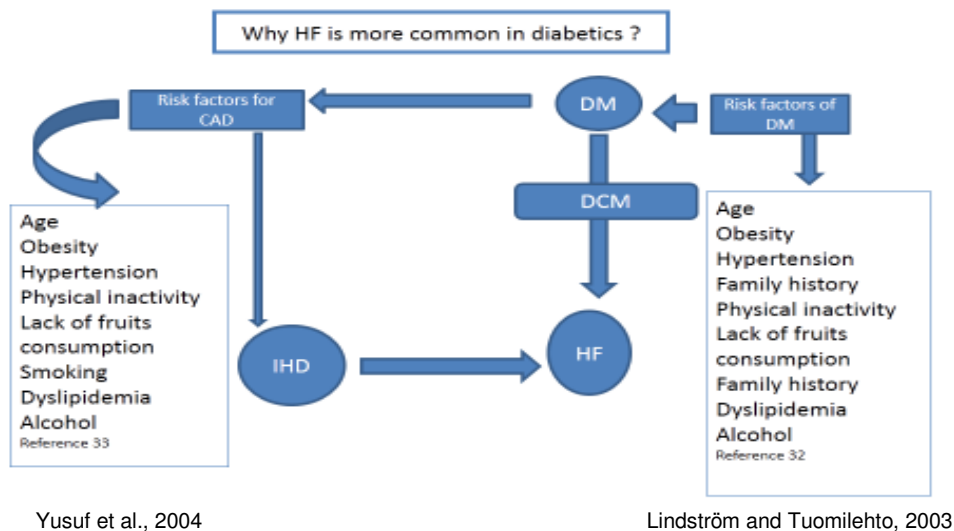
DM is clearly known as a risk factor for poor cardiovascular outcome. What is less appreciated by physicians and still considered somewhat controversial by some cardiologists is the concept that DM affects cardiac structure and function independently of blood pressure or CAD. The following evidence strengthens the concept of DCM as an independent medical condition.

First, the 2013 ACCF/AHA Guideline for the Management of HF (Yancy et al., 2013) considered DM as stage A, predicting the need for the prevention and early treatment of HF before it progresses to an advanced stage (Table 1). Diabetic patients with no previous cardiovascular disease had the same long-term mortality as non-diabetic patients with established CAD (Haffner et al., 1998).

Malmberg K et al. confirmed the same facts in OASIS registry. (Malmberg et al., 2000). These data gave us the concept that DM had its own impact on poor cardiovascular outcome in the absence of CAD. Despite a comparable infarct size, diabetic patients have a far greater risk of developing HF post-myocardial infarction (MI) compared with non-diabetic patients (Kouvaras et al., 1988; Jaffe et al., 1984). This is explained by a lack of normal response in DM following MI: the surviving myocardium of non-diabetic patients becomes hyperkinetic to compensate for non-viable infarcted myocardium in an attempt to maintain cardiac output; however, in diabetic patients, these areas of myocardium cannot achieve this compensatory enhancement in function due to a complex set of intra- and extra-myocardial factors superimposed on an already reduced coronary artery flow reserve (Nahser et al., 1995). In

Table 2. Prevalence of diabetic patients in HF studies.

Study name (reference)	Total no. of patients	Percentage of diabetics (%)
ADHERE (Adams et al., 2005)	187,565	44
EHFS- II (Nieminen et al., 2006)	3,580	33
GULF CARE (Sulaiman et al., 2015)	5,005	50
EMPHASIS – HF (Zannad et al., 2011)	2,737	34
ATLAS (Ryden et al., 2000)	3,164	19
SOLVD (Shindler et al., 1996)	2,569	26
HEARTS n (AlHabib et al., 2014)	2,610	64.1
RO-AHFS (Chioncel et al., 2011)	3,224	33
EPHESUS TRIAL (Pitt et al., 2003)	6,632	32
ATTEND (Sato et al., 2010)	1110	34
KOREAN H.F. REGISTRY (Youn et al., 2012)	1,527	31.4
ITALIAN AHF (Tavazzi et al., 2006)	2,807	38
OPTIMIZE-HF (Fonarow et al., 2004)	48,612	42

**Figure 1.** Relation between DM and HF

addition, impaired augmentation of left ventricular ejection fraction (LVEF) occurs in as many as 40% of patients with diabetes (Scognamiglio et al., 1998).

Second, the prevalence of DM in HF populations was overrepresented, varying from 20% to 60% (Table 2) compared with a prevalence of 4-6% in the general population.

The explanation is summarized in Figure 1, where DM is a direct cause of cardiomyopathy and HF, as well as a risk factor for the development of CAD, which is the most common cause of HF.

Third, the similarity of the risk factors for development of DM (Lindström and Tuomilehto, 2003) and risk factors for development of CAD (Yusuf et al., 2004) may explain the high prevalence of HF in DM. There is a relationship between microvascular complications and idiopathic cardiomyopathy (ICM) based upon a study that showed

that DM is more likely to have ICM compared to non-diabetes. The relative odds (RO) were 1.44 in non-complicated DM, 1.54 in DM complicated by macrovascular disease, and 2.74 in DM with microvascular complications. This study concluded that diabetes was independently associated with ICM in the general U.S. population (Bertoni et al., 2003). In addition, microangiopathic changes in the small vessels of the heart of diabetic patients may contribute to DCM (Van Hoven and Factor, 1989).

2 Pathophysiology of diabetic cardiomyopathy

A clear understanding of the pathophysiologic mechanisms of DCM cardiomyopathy is still lacking. However, several pathophysiologic disorders have been proposed to explain the structural and functional changes

associated with DCM. These processes are not mutually exclusive and likely act synergistically to give rise to DCM. Hyperglycemia is a central driver in the pathophysiology of DCM because it can trigger several biological and cellular responses that occur in DCM. The following paragraphs will discuss the possible underline mechanism of diabetic cardiomyopathy under **Nitric oxide, endothelial dysfunction and micro-angiopath, oxidative stress, fatty acid and Diabetic cardiomyopathy, cardiac autonomic neuropathy (CAN), myocardial cell hypertrophy, Renin Angiotensin Aldosterone System (RAAS)** and treatment available for diabetic patient with HF secondary to diabetic cardiomyopathy.

3.1 Nitric oxide, endothelial dysfunction and microangiopathy

Hyperglycemia leads to impairment of endothelial cell nitric oxide (NO) production, which results in the endothelial dysfunctions that play a major part in the development of DCM. By means of protein kinase C (PKC)-mediated pathways, hyperglycemia paradoxically alters the function of endothelial nitric oxide synthase (eNOS) such that it acts as a superoxide generator that then becomes systematically activated in the entire vascular bed, regardless of the absence of atherosclerotic lesions (Guzik et al., 2002).

Hyperglycemia increases production of vasoconstrictor prostaglandins and glycated proteins such as PKC, an intracellular signaling molecule activated in diabetes and can lead to endothelial dysfunction by reducing the bioavailability of nitric oxide while increasing oxygen-derived free radical production (Aneja et al., 2008).

Moreover, free radicals are potent stimulators of the programmed cell death that is substantially enhanced in diabetic hearts (Young et al., 2002).

Hyperglycemia also increases endothelium adhesion molecules and platelet and vascular growth factors that cumulatively enhance vasomotor tone and vascular permeability, limiting growth and remodeling (Poston and Taylor, 1995; Tesfamariam et al., 1991). Endothelial dysfunction not only causes atherosclerosis but also reduces the development of collateral vessels.

Hyperglycemia is associated with characteristic changes in the microvascular architecture that share endothelial dysfunction mechanisms. These changes include abnormal capillary permeability, microaneurysm formation, subendothelial matrix deposition, and formation of fibrosis surrounding arterioles (Aneja et al., 2008). These changes occur in diabetic nephropathy, neuropathy, and retinopathy. Impaired coronary microvasculature is frequently observed in patients with type 2 diabetes mellitus (DM), insulin resistance, and DCM (Factor et al., 1984). This defect is caused by reduced levels of bioavailable nitric oxide (Zhou et al., 2010).

Vascular endothelial growth factor is a critical mediator of angiogenesis and arteriogenesis. Decreases in these proangiogenic proteins are associated with microvascular endothelial cell apoptosis and endothelial dysfunction (Boudina and Abel, 2007).

3.2 Oxidative stress

Reactive oxygen species (ROS) which produced by hyperglycemia is responsible for development of DCM (Nishikawa et al., 2000), through changes in excitations contractions coupling of myocardial cell (Amour et al., 2004).

The ROS production in the heart of diabetic patients mechanistically is unknown. However some studies proposed that free fatty acids (FA) promote productions of ROS (Boudina and Abel, 2010).

The excess PKC-isoform produced by high ROS will cause endothelial dysfunction and subsequently DCM (Koya and King, 1998).

3.3 Fatty acid and Diabetic cardiomyopathy

In non-DM, the energy required for cardiac contraction comes equally from glucose metabolism and free fatty acids (FFAs) (Rodrigues et al., 1998).

In DM, the reduced glucose uptake caused by cardiac and systemic insulin resistance promotes a substrate shift toward increased FFA oxidation, resulting in reduced cardiac efficiency of muscle fiber function in response to electrical stimuli (Mandavia et al., 2012).

Lipotoxicity of the myocardium results from reduced lipid oxidations (McGavock et al., 2006). Additionally ceramide production from the lipid as intermediate product may cause cardiac dysfunction through apoptosis (Zhou et al., 2000)

Localized ^1H magnetic resonance spectroscopy (^1H -MR spectroscopy) in DM demonstrated cardiac steatosis (increased intracellular triglycerides in the myocardium), which preceded the functional impairment of the myocardium in the form of diastolic but not systolic dysfunction (McGavock et al., 2007).

3.4 Cardiac autonomic neuropathy (CAN)

Diabetic autonomic neuropathy can lead to changes in sympathetic innervation and subsequent disordered adrenergic receptor expression and altered catecholamine levels in the myocardium. The increased expression of the beta-1-receptor resulted in enhanced apoptosis, fibrosis, hypertrophy, and impaired myocardial function (Bisognano et al., 2000).

Autonomic neuropathy manifests early by tachycardia, but with disease progression and involvement of both the sympathetic and parasympathetic nervous systems, heart rate becomes fixed and unresponsive to exercise, stress, or sleep. These findings suggest complete sympathetic

and parasympathetic cardiac denervation, which may lead to the development of DCM (Vinik and Ziegler, 2007).

Ventricular filling abnormalities (diastolic dysfunction) are most prominent in patients with autonomic neuropathy (Airaksinen et al., 1989).

Impairment of cardiac sympathetic innervation manifests as abnormal responses to exercise in the early phase of DCM in the form of defective (blunted) recruitment of myocardial contractility in determining left ventricular (LV) dysfunction during exercise, despite normal contractile reserve (Scognamiglio et al., 1998).

3.5 Myocardial cell hypertrophy

In a multiethnic population, the likelihood of having LV mass that exceeds the 75th percentile is greater in patients with type 2 diabetes, after adjusting for various covariates including hypertension (Eguchi et al., 2008). Increased LV mass is an independent risk factor for HF that may occur independently of arterial blood pressure in type 2 diabetes (Aneja et al., 2008). In the initial stages, patients with DCM may be asymptomatic or may have only mild exercise intolerance that eventually progresses to HF (Owan et al., 2006). The early change in DCM is diastolic dysfunction. It progresses further to systolic dysfunction and then to overt HF (Owan et al., 2006).

3.6 Renin Angiotensin Aldosterone System (RAAS)

Hyperglycemia-enhanced activity of the local RAAS that induces functional abnormalities in ventricular myocytes (Falcão-Pires and Leite-Moreira, 2012) has been shown to be associated with increased oxidative damage and cardiomyocyte and endothelial cell apoptosis and necrosis in diabetic hearts (Frustaci et al., 2000).

4 Treatment of diabetic cardiomyopathy

Lifestyle modifications is the first line intervention in the treatment of DM, it is recommended by all advisory associations like American Diabetic Association (ADA) and the European Association for the Study of Diabetes (EASD).

The lifestyle modification may work as a physiological adaptations for the early metabolic changes and it should be the ultimate intervention to prevent diabetes progression. They also recommend, when appropriate, to reduce A1c to <7.0%. Such interventions include low-carbohydrate diet, weight loss and increased physical activity.

In the advanced stage of diabetic complications where degenerative changes occur, the reversal of the process become dismal and the early stage of DCM in the form of diastolic dysfunction will institute where no specific therapy are available.

If lifestyle changes fail or are not sufficient, the guidelines generally agree that the initial pharmacological agent should be metformin (Tashko, 2017). However when HF is well established and drugs therapy is required particularly in the presence of comorbid conditions like renal dysfunction the lactic acidosis become an important side effect of metformin.

Observational study reported possible survival benefits of metformin with reasonable safety (Eurich et al., 2005). Uses of metformin in ambulatory HF diabetic patients reported mortality reduction (Aguilar et al., 2011).

The integration of care to ensure the lifestyle modification as early as possible and control hyperglycemia, blood pressure, lipid profiles and other precipitating factors.

DCM is associated with coronary perivascular fibrosis, cardiac hypertrophy, interstitial fibrosis and myocardial mechanical dysfunction these changes can be ameliorated by uses of angiotensin converting enzyme inhibitors (ACEI) (Al-Shafei et al., 2002). In ATLAS study, higher dose of ACEI reduces mortality compared to lower dose (Ryden et al., 2000). Alternatively candesartan improved the echocardiographic parameters of diastolic dysfunction and reduced collagen synthesis in diabetic patients without symptoms (Kawasaki et al., 2007). Cardiac hypertrophy and fibrosis in HF patients reported to be reduced by aldosterone antagonist therapy (Orea-Tejeda et al., 2007).

For beta blockers (BB) used in the CIBIS II trial, the efficacy was similar in diabetic and non-diabetic patients with respect to all mortality/morbidity endpoints (Erdmann et al., 2001).

It is clear that most of the drugs useful in HF had greater or equivalent benefits in diabetic patients with HF.

5 Anti-diabetic medications in cardiac patients

Recently, a few classes of new anti-diabetic medications demonstrated either neutral or beneficial effects on cardiovascular outcomes. However, older drugs such as sulfonylureas, as opposed to metformin for initial treatment of diabetes, were associated with an increased hazard of CVD events or death (Roumie et al., 2012). Fewer deaths occurred in metformin users, alone or in combination with sulfonylureas, compared with sulfonylurea monotherapy (Evans et al., 2010).

5.1 Thiazolidinediones (TZDs)

Thiazolidinediones work by targeting the agonist of Peroxisome-Proliferator-Activated Receptors gamma (PPAR-gamma) receptor that activates a number of genes in the body and plays an important role in how the body metabolizes glucose and body fat. Two drugs have been used in this class: pioglitazone and rosiglitazone.

Rosiglitazone has been banned because of increased risk of cardiovascular events in the form of MI and HF, compared to pioglitazone, which is safer but should be used with caution in HF patients (Nissen and Wolski, 2007; Psaty and Furberg, 2007; Chen et al., 2012).

5.2 Dipeptidyl peptidase 4 (DPP-4) inhibitors:

This class of drugs works by prolonging the action of incretin hormones, including glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, by inhibiting their breakdown. Three previous cardiovascular outcome trials of DPP4 inhibitors did not show an increase or a decrease in the number of major adverse cardiovascular events (Scirica et al., 2013; White et al., 2013) but raised concern regarding recurrent admission for HF. For the effects of sitagliptin on cardiovascular outcome in type 2 diabetes, the TECOS study confirmed no increased or decreased in cardiovascular outcome (White et al., 2013). Meta-analysis of randomized, controlled trials suggested an increase of 24 to 25% in the risk of cardiovascular events associated with these agents (Udell et al., 2015; Clifton, 2014).

5.3 Sodium Glucose Linked Transporter (SGLT) inhibitor:

The Sodium Glucose-Linked Transporter (SGLT), located in proximal renal tubules, causes renal glucose reabsorption. SGLT-2 is responsible for 90% of glucose reabsorption compared to 10% for SGLT-1 (Kanai et al., 1994). Inhibiting this reabsorption of glucose leads to serum glucose reduction.

SGLT-2 inhibitors include empagliflozin (Jardiance), canagliflozin (Invokana) and dapagliflozin (Forxiga).

Empagliflozin reduces cardiovascular events and mortality in type 2 diabetes compared to standard care, in addition to reducing recurrent admission for HF (Zinman et al., 2015). Similarly, canagliflozin showed reduced cardiovascular outcomes, reduced recurrent admission for HF and reduced renal events in type 2 diabetes. However, there was more amputation in the treated group compared to the placebo (Neal et al., 2017).

5.4 Incretin: glucagon-like peptide-1 receptor agonists (GLP-1RA):

This class includes exenatide, liraglutide (Victoza, Saxenda), albiglutide (Tanzeum), dulaglutide (Trulicity) and lixisenatide (Lyxumia). They stimulate insulin and suppress glucagon secretion, inhibit gastric emptying, and reduce appetite and food intake. An example of this class is liraglutide, which was studied in type 2 diabetes versus placebo and standard of care in a time-to-event analysis. The rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was lower with liraglutide than with the

placebo. However, it was neutral for HF (Marso et al., 2016).

CONCLUSIONS

Diabetic cardiomyopathy (DCM) is a separate entity in DM patients with HF in the absence of known etiology such as CAD, hypertension congenital or valvular heart disease. Multiple factors are involved, including oxidative stress, endothelial dysfunction, microangiopathy, fatty acids, autonomic neuropathy, myocardial cell hypertrophy and excessive activation of RAAS. These commonly lead initially to diastolic dysfunction that becomes symptomatic or asymptomatic and then progresses to systolic dysfunction. Treatment should include all proven evidence-based medicine treatment including ACEI, ARBs, BB, mineralocorticoid receptors antagonists (MRA) and symptomatic treatment. With regard to hypoglycemic agents, metformin, some TZDs such as pioglitazone, DPP-4 inhibitors such as sitagliptin, Sodium Glucose-Linked Transporter inhibitors (SGLT-2 i) such as empagliflozin, incretin hormone, and glucagon-like peptide-1 receptor agonists (GLP-1RA) such as liraglutide. Further outcome trials on cardiovascular events will add more information in this respect.

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