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Review Article

Diabetic Related Cardiomyopathy, Pathophysiology, Diagnosis and Potential Treatments

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Abstract

Patients with diabetes mellitus are at increased risk of heart failure irrespective of presence of other heart failure causes like CAD or hypertension. This cardiomyopathy is called diabetic cardiomyopathy (DCM), the detection of which is challenging since most of diabetic patients have other risk factors for developing heart failure. The exact causing pathological mechanism of DCM is unknown but possible mechanisms are related mainly to hyperglycemia leading to many changes like increase free fatty acids, microvascular disease, cellular fibrosis and apoptosis. There is no specific treatment to patients with heart failure related to DMC. Currently there are new medical treatment for type II DM like GLP-1 receptor agonists (GLP-1RA) and Sodium-glucose transporter type 2 (SGLT2) inhibitors that has been shown to decrease the risk of atherosclerotic cardiac diseases in diabetic patients and subsequently heart failure.

Keywords: *Diabetes Mellitus; Cardiomyopathy; Pathophysiology*

Introduction

A cardiomyopathy is defined cardiac muscle disorder that affect the heart function in the absence of other known causes of heart failure like coronary artery disease, hypertension, valvular heart disease, or congenital heart disorders [1]. Diabetic cardiomyopathy has two main phenotypes, a dilated/HFREF (heart failure with reduced ejection fraction) phenotype. And a restrictive/HFPEF (heart failure with preserved ejection fraction) phenotype. The two phenotypes may co-exist in patients with heart failure which starts with microvascular disease of coronaries and ends up with cellular death [2].

DM is an important and very common risk factor for coronary atherosclerosis leading to ischemic heart disease (IHD) and subsequently to heart failure. But it has also been shown that diabetes can cause heart failure without presence of (IHD) by causing diabetic related cardiomyopathy. In heart failure patients, DM is one of independent risk factors of worse outcomes, short- and long-term mortality [3]. Furthermore, It is reported that there are poor prognosis and high-risk mortality associated with diabetes and ischemic cardiomyopathy, while there was no association between diabetes mellitus and mortality risk in those with non-ischemic cardiomyopathy [4) However, two studies found diabetes to be associated with an increased mortality rate only in the non-ischemic heart failure subgroup [5]. Moreover, a review done in Germany shows worse prognosis in patients with idiopathic dilated cardiomyopathy compared to those with ischemic cardiomyopathy [6]. On the other hand a study in Denmark showed that Ischemic cardiomyopathy and non-ischemic cardiomyopathy have an equal long term prognosis patients with diabetes mellitus [7]. In regards the underlying mechanism of DCM is less understood however multiple postulated theories was assumed to contribute to the etiology of DCM development including microvascular endothe-

lial dysfunction and myocardial inflammation, fibrosis and hypertrophy [8]. Most of clinical trials examined the relation between DM and IHD, prognosis in details but limited data exists on this unique Diabetic related cardiomyopathy, its mechanism, pathophysiology, clinical presentation management and prognosis in heart failure patients [9].

So, the objective of this review to present the definition of diabetic related cardiomyopathy (DMCM), pathophysiology, clinical presentation, specific management in patients with DM and heart failure irrespective of ischemic heart disease and hypertension.

Definition, prevalence and characteristics of diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is a unique cardiac manifestation of patients with diabetes characterized by left ventricular hypertrophy and diastolic dysfunction in the early stages and progress to overt heart failure with reduced systolic function in the advanced stages. The prevalence of diabetes mellitus is rapidly increasing over the years worldwide. Diabetes mellitus is the leading cause of atherosclerotic vascular disease, which result in myocardial infarction, stroke, and peripheral vascular disease. DCM characterized initially with diastolic dysfunction due to left ventricle hypertrophy and fibrosis leading to myocardial stiffness and subsequent elevated LV filling pressure. Rubler., *et al*. has introduced the term diabetic cardiomyopathy 30 years ago [10], in four patients with DM and heart failure diabetic patients with heart failure and normal coronary system. Since then, DCM is defined as ventricular systolic abnormality in absence of coronary artery disease and hypertension. Studies have shown that DM can cause cardiac hypertrophy, fibrosis and myocardial stiffness, regardless of presence of hypertension [11]. This association supports the idea of presence of this unique disease of DCM.

So, it is thought that the disease of DCM course stays subclinical, for long time in which cellular changes and fibrosis happen leading to asymptomatic diastolic dysfunction, then progress to symptomatic clinical systolic heart failure. The exact timing of when this transition happens is unknown. In one study, they found that patients with diastolic dysfunction in echocardiogram develop clinical HF after a 6-year follow-up [12].

Doppler Echocardiogram studies have shown that patients with diabetes have an evidence of underlying subclinical left ventricle dysfunction by looking at different diastolic parameters [13].

In patients with type I DM, the prevalence described for myocardial dysfunction in a recent study performed in 1093 patients was 15.5% (1.7% with LVEF <45%, and 14.4% with evidence of diastolic dysfunction) [14]. Whether screening and aggressive management of diabetic patients with preclinical diastolic dysfunction might delay the progression to HF with improved outcomes is not yet known. Early recognition and management of HF symptoms delays the progression of the disease and improves long term outcomes in diabetic patients since DM worsen the prognosis of HF. Echocardiography might be warranted, especially in the presence of poor glycemic control, long duration of diabetes, an adverse risk factor profile or micro/macro albuminuria.

Pathophysiologic mechanisms of diabetic cardiomyopathy

A clear understanding of the precise pathophysiologic mechanisms of diabetic cardiomyopathy is still lacking. However, multiple mechanisms have been postulated to explain how diabetes affects the cardiovascular system (Figure 1). Hyperglycemia is considered to be a central driver in the pathophysiology of diabetic cardiomyopathy because it can trigger several adaptive and maladaptive responses that are evident in diabetic cardiomyopathy. We describe several known mechanisms that have been demonstrated [15].

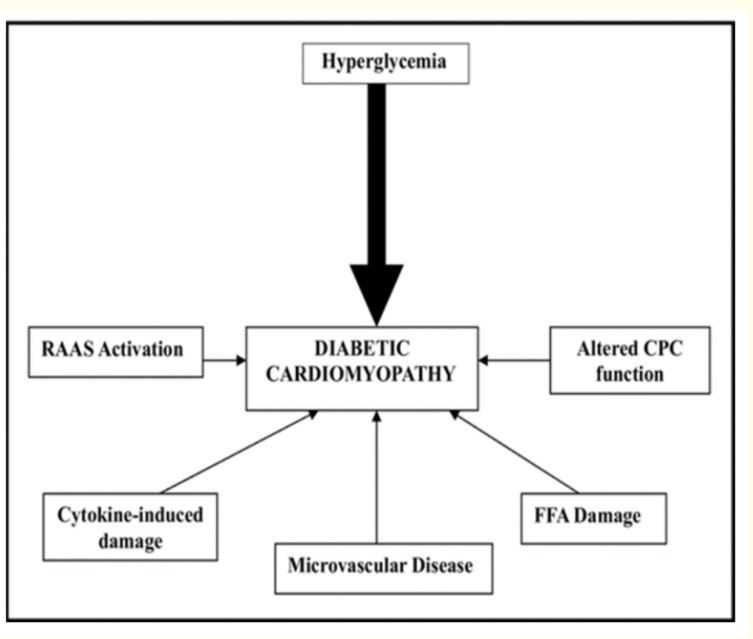

Figure 1: *Pathogenesis of diabetic cardiomyopathy.*
FFA= Free Fatty Acid; CPC= Cardiac Progenitor Cells; RAAS= Renin-angiotensin-aldosterone System.

Free fatty acid metabolism disturbances

In normal subjects, most of the energy required for myocardium activity is usually derived from both glucose metabolism and free fatty acids (FFA); but in diabetes mellitus, reduction of glucose protien transporters will occur so most of the myocarial energy come from FFA. Elevation of circulating FFA levels play a major role in the pathogenesis of diabetes. FFA metabolism could be an important contributor to abnormal myocardial cell function in patints with diabetes.

It increses periheral insulin resistance and increase oxygen requirement which in turn leads to accumaulation of intracellualr toxic intermediates of FFA. FFA also inhibits an enzyme called pyruvate dehydrogenase which inhibits pyruavte and glucos utilization, this impairs production of myocardial energy with subsequent accumulation of glycolytic intermediates, as shown in figure 2 [16]. Furthermore, these toxic intermediates (Lipotoxic intermediates) resulting from FFA metabolism can interfere with myocyte calcium handling which impairs myocardial contractility at the cellular level [17].

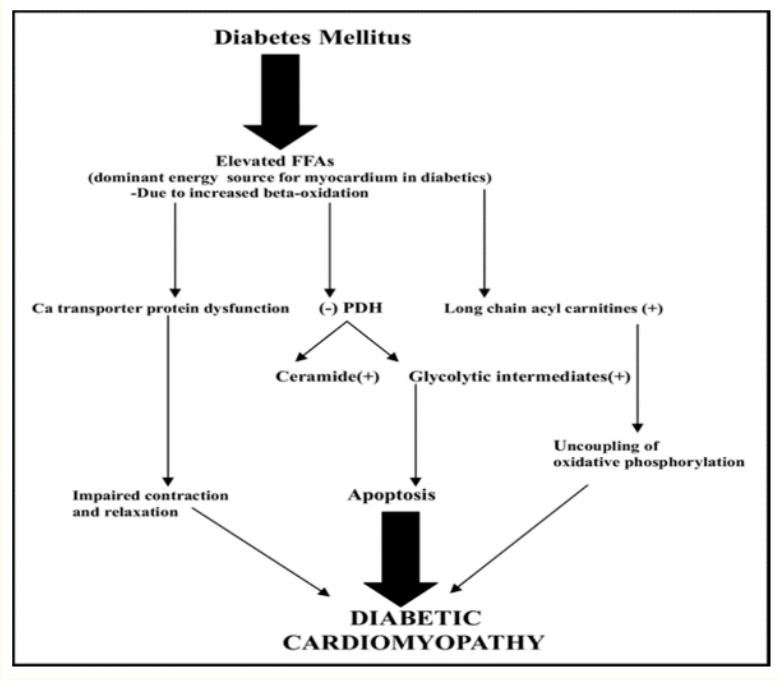

Figure 2: *The role of altered myocardial metabolism in the development of diabetic cardiomyopathy. FFA= Free Fatty Acid; PDH= Pyruvate Dehydrogenase; Ca= Calcium.*

Increased apoptosis

Studies suggest that hyperglycemia results in production of reactive oxygen radicles, contributing to accelerated apoptosis. Myocardial cell death by apoptosis is directly related to interaction of hyperglycemia and renin-angiotensin system (RAS). Activation of the (RAS) leads increased oxidative stress with subsequent necrosis of myocardial and endothelial cells in the hearts of patients with diabetes and end stage heart failure, thereby representing another potential mechanism for cell death. It is unclear, whether increased apoptosis is a cause or a result of diabetic cardiomyopathy [18].

Increased myocardial necrosis and fibrosis

In histological examination, myocardial fibrosis and collagen deposition constitute the main structural changes in patients with DCM. The main underlying pathophysiology leads to these changes is activation of RAS system as well as endothelial dysfunction In turn these changes will cause myocardial hypertrophy, perivascular fibrosis and thickening of endothelial walls [19].

A process of binding of glucose to collagen called glycated collagen leads to stiffness of cardiac tissue and endothelial wall stiffness as well which leads to atherosclerosis.

Furthermore, end products of glycation also contribute to intracellular oxidative stress, which can contribute to cell damage [20]. Subsequently this leads to impaired LV function (both diastolic and systolic). Moreover, hyperglycemia and hyperinsulinemia stimulate overexpression of transforming growth factor-_1 by cardiac fibroblasts, resulting in fibrous tissue deposition [21], which also contribute to myocardial dysfunction.

Microvascular disease and endothelial dysfunction

Diabetes can cause changes in microvascular system. The fibrous tissue formation and collagen formation leads to small vessel wall stiffness so even in the absence of obstructive coronary artery disease, those patients will have reduction of coronary blood flow reserve [22]. Microangiopathy happens as a result from endothelial dysfunction, hormonal disturbance and altered cardiac cell metabolism. Vasoconstriction is also caused by enhanced synthesis of vasoconstrictor prostanoids and activation of protein kinase C [23]. Protein kinase C, reduces the bioavailability of nitric oxide while increases oxygen-derived free radical production. Therefore, activation of this enzyme plays an important role in the development of microvascular complications of other body systems in diabetic patients, as seen in diabetic neuropathy and nephropathy. Hyperglycemia, hyperlipidemia and activation of RAS system promotes microangiopathy as well [24].

Autonomic neuropathy

Diabetic autonomic neuropathy can lead to changes in sympathetic innervations and subsequent disordered adrenergic receptor expression and altered catecholamine levels Enhanced presentation of B1 receptors in the myocardium results in fibrosis, apoptosis and impaired myocardial function [25].

Activation of the renin-angiotensin system (RAS)

Activation of RAS is one of the most important factors leading to cardiomyopathy. Angiotensin II receptor density and mRNA are elevated in the diabetic heart [26]. Activation of the RAS in diabetics is associated with increased oxidative damage and cardiac cells and endothelial cell with subsequent necrosis in diabetic hearts. Activation of RAAS in the myocardium promotes remodeling processes which leads to dilated left ventricle with irreversible myocardial dysfunction if not treated early. Inhibition of the renin angiotensin system was shown to reduce the production of reactive oxygen species (ROS) diabetic rats [27].

Increased oxidative stress

production of ROS is an important player in the development and the progression of diabetic cardiomyopathy [28] (Figure 3). It leads to increased oxidative stress in diabetic hearts. Tissues that are exposed to hyperglycemia noticed to have increased mitochondrial ROS generation. Increased ROS generation leads to cell death and increased apoptosis, which could contribute to the pathogenesis of diabetic cardiomyopathy [29]. Thus, increased ROS-mediated cell death could promote abnormal cardiac remodeling, which subsequently may contribute to the structural and functional changes that are associated with diabetic cardiomyopathy. Moreover, Increased ROS contributes to hyperglycemia-induced activation of protein kinase C isoforms, increased formation of glycation end products [30], which may all lead to the development of cardiac complications in diabetes mellitus. Thus, ways that either reduce ROS or increase myocardial antioxidant defense mechanisms might have therapeutic efficacy in improving myocardial performance in diabetes mellitus.

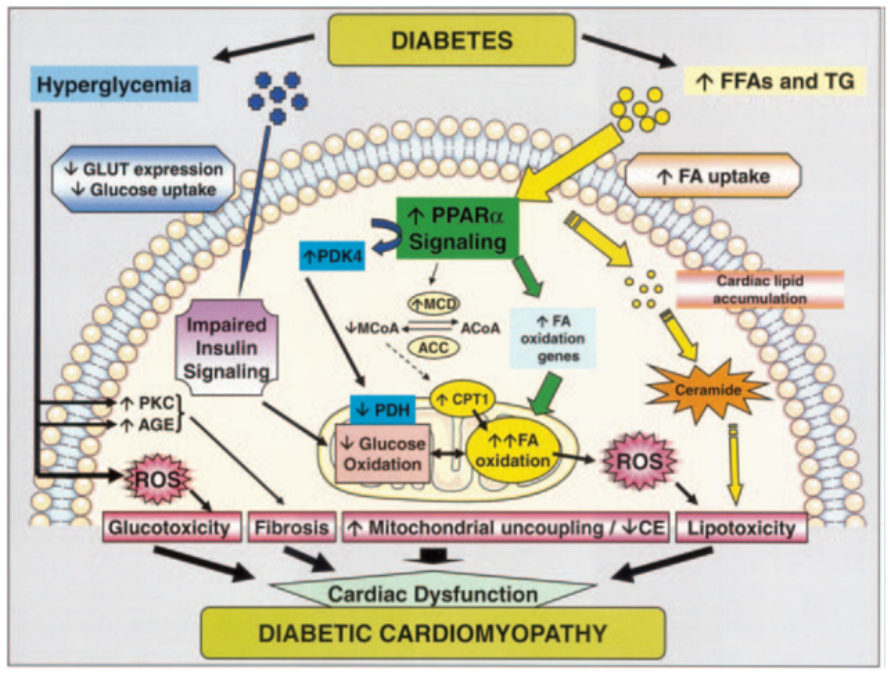

Figure 3: *Potential contributors to the development of diabetic cardiomyopathy.*

Pathogenesis of diabetic cardiomyopathy, including lipotoxicity, cell death, and tissue damage, as well as mitochondrial uncoupling and reduced cardiac efficiency.

TG indicates triglycerides; GLUTs, glucose transporters; PDK4, pyruvate dehydrogenase kinase 4; MCD, malonyl-coenzyme A decarboxylase; MCo A, malonyl coenzyme A; ACoA, acetyl-coenzyme A; ACC, acetyl coenzyme A carboxylase; CPT1, carnitine palmitoyl-transferase 1; PDH, pyruvate dehydrogenase; CE, cardiac efficiency; PKC, protein kinase C; and AGE, glycation end products.

Impaired calcium homeostasis

Intracellular calcium (Ca) is an important player in cardiac contractility. Alteration of Calcium and other ion homeostasis was observed in diabetic myocardial cells. This can happen by reducing ATPase activity [31] decreased uptake of Ca by SR calcium, and reduction of Na-Ca exchange. sarcolemma Ca ATPase. The SR Ca store and rates of Ca release and reuptake into SR were depressed in type 1 diabetic rat myocytes. The rate of Ca efflux via sarcolemma Na-Ca2 exchanger also was depressed. In the mouse model of type 2 diabetes mellitus, Ca efflux in the cardiomyocyte was reduced, SR Ca load was depressed, ryanodine receptor expression was reduced [32].

Technical challenges are involved in performing similar studies in humans. Human Studies focused on examining changes in expression levels of genes involved in calcium signaling in cardio myocytes isolated from failing hearts of transplant recipients [33].

This is not studied yet in diabetic patients. A recent study described depressed myocardial function as a result of decreased Ca sensitivity obtained from diabetic patients at the time of cardiac surgery [34]. This limited clinical study supports previous studies in animals, however exact mechanisms responsible for altered calcium handling in patients with diabetic cardiomyopathy still to be studied further in human subjects

Diagnosis of diabetic cardiomyopathy

Diagnosis of DCM clinically could be challenging since all other causes of cardiomyopathy like IHD, HTN and valvular heart diseases should be excluded. Another challenge is the lack of any pathognomonic histologic changes or specific imaging characteristics associated with the diagnosis of DCM. The diagnosis of diabetic cardiomyopathy mainly relies on echocardiographic imaging techniques that can demonstrate left ventricle systolic and diastolic dysfunction. Endomyocardial biopsies are not indicated since it is an invasive test so it is not practical to be done in all diabetic patients with heart failure.

The echocardiographic features of either systolic or diastolic dysfunction is often confirmatory. However, in the absence of overt HF symptoms, an imaging diagnosis is warranted. There is still no consensus in the precise imaging definition of diabetic cardiomyopathy. A proposed Imaging definition for diabetic cardiomyopathy includes either or both features listed as follows:

- Evidence of cardiac hypertrophy and left atrial dilatation determined by echocardiography or cardiac magnetic resonance imaging;
- Abnormal diastolic parameters with doppler evidence of elevated Left ventricle filling pressure using Mitral inflow pulse doppler and tissue doppler imaging. Also strain imaging can be used to detect sub clinical disease.

Evidence of cardiac hypertrophy

Presence of Left ventricle hypertrophy (LVH) although not specific for DCM however its presence represents the main findings of DCM and usually indicates more advanced stages of the disease. Not all patients with LVH will have doppler evidence of LV diastolic dysfunction. The emerging new imaging techniques like cardiac magnetic resonance (CMRI) has improved our understanding of DCM. CMRI shows fatty or fibrosis infiltrates in the hypertrophied myocardium, as well as alteration in the myocardial geometry and increases in ventricular mass. Weather LVH of DCM regresses after therapeutic interventions is still to be studied.

Evidence of left ventricular diastolic dysfunction

Abnormalities in mitral pulse Doppler inflow patterns were associated with poor glycemic control and presence of cardiac structure abnormalities [35,36]. furthermore it was found that better glycemic control could lead to reversible changes of diastolic dysfunction in early stages of the disease [37].

Tissue doppler imaging TDI usually assess the movements of the mitral valve by Doppler imaging signals of myocardial tissue at the mitral annulus. By using a combination of trans mitral forward signal (E) and TDI indices (e'), the ratio of mitral E/e' has been used to detect Left ventricle filling pressure and LV compliance. TDI studies can be used also for unrevealing subclinical disease in asymptomatic diabetic patients [38].

One important but often overlooked structural indicator of diastolic dysfunction is the presence of left atrial enlargement, often present in patients with diastolic dysfunction.

However, studies have not specifically evaluated the value of this parameter in diabetic cardiomyopathy. microvascular disease in the absence of significant CAD may lead to significant diastolic dysfunction and diastolic heart failure. Use of speckle-tracking or strain imaging, has provided even greater insights into early manifestations of myocardial dysfunction that may be "precursors" of the development of diabetic cardiomyopathy at earlier stages.

Medical therapy for heart failure in patients with diabetes

Current guidelines from the European (39) as well as the American (ACC/AHA task force members 2016) [40] cardiology societies do not recommend specific treatment approaches in heart failure patients with diabetes. so patients with DM and heart failure are treated with the same regimens used for heart failure in general besides the medications used for glycemic control. In this review will cover mainly the specific antidiabetic treatment that have an effect on heart failure and we will not discuss heart failure medical therapy since it is outside the scope of this review.

Glycemic control medications

A good glycemic control could be beneficial in the early stages of myocardial dysfunction although the evidence is limited. Studies have shown that diabetic cardiomyopathy does not develop in patients with well controlled type 1 diabetes, which supports the role of uncontrolled hyperglycemia in the pathogenesis of DCM [41] Hyperglycemia also leads to microvascular complications in diabetes, which in turn contribute significantly to the pathogenesis of diabetic cardiomyopathy, so good glycemic control prevents those complications and perhaps the most important step in the overall management of diabetic cardiomyopathy specially early in the course of the disease.

There is no evidence of which is the best anti glycemic medication should be used to delay or prevent DCM. It was found in some studies that, glucagon-like peptide-1 analogues have demonstrated improved diastolic parameters in diabetic patients without overt heart failure. Moreover these agents also have shown Improved cardiac function in post infarction as well as populations with heart failure [42]. The choice of antidiabetic therapy in patients with DCM is determined by their clinical profile such as age, renal dysfunction, hypoglycemia risk, and concomitant drug therapy regardless presence or absence of heart failure symptoms and signs. Some antidiabetic medications have been specifically studied in HF patients.

Metformin

Currently, the main clinical practice guidelines recommend the use of metformin as the initial therapy of choice in the vast majority of patients with T2D. There are no data from randomized trials specifically designed to evaluate the effects of metformin on HF, either on incident HF or on safety and efficacy in patients with established HF. However, metformin is at least as safe as other hypoglycemic agents in patients with DM and HF, even in those cases with decreased ejection fraction [43]. Moreover, data from these observational studies showed that metformin leads to a reduction in all-cause mortality in patients with T2D with congestive HF and appears to reduce the admissions from congestive HF in patients with congestive HF or with moderate chronic nephropathy. So metformin is considered as the first-line therapy in clinically stable subjects with mild or moderate left ventricle systolic dysfunction without overt signs of acute heart failure.

Sulfonylureas and insulin

As with metformin, clinical trial data are scarce concerning the impact on HF in subjects with established cardiovascular disease treated with either sulfonylureas or insulin. In newly diagnosed type 2 DM, the UK Prospective Diabetes Study (UKPDS) showed no difference in HF events or risk of other diabetic complications comparing sulfonylureas or insulin with dietary intervention [44]. Diagnosis of HF it is not a contraindication for sulfonylurea therapy use, but an alternative option of using metformin seems preferable. The reason for this the risk of hypoglycemia associated with sulfonylureas and insulin in heart failure patients.

Thiazolidinediones

The thiazolidinedione (TZD) initially was thought to have a beneficial cardiovascular effects, however, the utility of TZDs in T2D has declined in the past decade, largely due to concomitant adverse effects of fluid retention and edema formation with worsening HF symp-

toms and signs. In Prospective Pioglitazone Clinical Trial in macro Vascular Events (PROactive), identified a substantial increase in risk of Heart failure [45]. In this study, There was a significant reduction in the secondary outcome of cardiovascular death, and non-fatal myocardial infarction or stroke, however there was no significant reduction in the primary endpoint, that included also re-vascularization procedures. So The European Society of Cardiology stated in their 2016 guidelines that thiazolidinediones are not recommended in any patient with HF [39].

Dipeptidyl peptidase IV (DPP-4) inhibitors

The cardiovascular effects of DPP-4 inhibitors remain controversial. The Data about these drugs are contradicting, some of them showed no effect on HF like sitagliptin and others showed the increased the risk of hospitalization for HF [46] so in general those drugs are not preferable in DCM if they presented with overt heart failure.

GLP-1 receptor agonists (GLP-1RA)

No increased risk of hospitalization for HF has been reported with GLP-1RAs in metanalyses of phase-II/III trials (exenatide, albiglutide, dulaglutide, liraglutide) [47] demonstrating the safety of this pharmacological class, and these findings have been confirmed in three large prospective cardiovascular outcome trials. Commonest of them Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Results (LEADER) with liraglutide which reported a trend towards a reduction in HF hospitalization together with a significant reduction in cardiovascular and all-cause mortality in patients with T2D at risk for cardiovascular disease.

Sodium-glucose transporter type 2 (SGLT2) inhibitors

the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus patients (EMPA-REG OUTCOME) trial was The first, randomized, controlled trial assessing CV safety in patients with T2D was, which was also the first clinical trial to demonstrate that, empagliflozin, not only safe in heart failure but also could reduce cardiovascular events [48]. The mechanism of empagliflozin is to inhibit sodium glucose cotransporter 2 (SGLT2), reducing glucose/sodium reabsorption, increase urinary glucose excretion and sodium delivery to distal tubules.

Results obtained in the EMPAREG trial showed that treatment with empagliflozin versus placebo, in addition to standard of care in subjects with T2D and high cardiovascular risk, is associated with significant reductions in the primary 3-point major adverse CV events outcome (a composite of CV death, non-fatal myocardial infarction and non-fatal stroke) (14% risk reduction), a 38% relative risk reduction in CV death, a 32% relative risk reduction in all-cause mortality and a 35% risk reduction in hospitalization for HF.

Empagliflozin has been shown to delay the progression of kidney disease and to reduce clinical renal events, including dialysis. Importantly, empagliflozin decreased the number of hospitalizations for HF and mortality by one-third. However, the mechanisms by which empagliflozin exerts CV protection are currently unknown. The early impact of empagliflozin on CV and hospitalization for HF suggest early hemodynamic effects of the drug. In addition, other potential mechanisms, such as weight loss, reduced blood pressure, sodium depletion, reduced oxidative stress, and arterial stiffness, as well as a reduction in sympathetic nerve activation, are shown by (Neal., *et al*. 2017) [49].

A large multinational study using real-world clinical practice databases from different countries compared hospitalization for HF and death in patients newly initiated on any SGLT-2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) versus other glucose-lowering drugs. The results obtained showed that treatment with SGLT-2- inhibitors was associated with a lower risk of HF and death, suggesting that the benefits seen with empagliflozin in a randomized trial might be a class effect applicable to a broad population of T2D patients in real-world practice (CVD-REAL).

Canagliflozin Cardiovascular Assessment Study (CANVAS) and the CANVAS renal end-points trial (CANVAS-R) have showed that the rate of the primary outcome, which is mainly CV death, MI and stroke, was lower in canagliflozin group compared to placebo group [50]. Recently, empagliflozin have shown an impressive results on both cardiovascular mortality and heart failure hospitalization in patients with HFpEF with 21 percent relative risk reduction [EMPEROR-Preserved] in which for the first time in eighteen years, a randomized prospective clinical trial has successfully shown a benefit of a medication that can reduce mortality and HF hospitalization in HFPEF patients weather diabetics or not [51].

Conclusion

In conclusion, the choice of a glucose lowering drug in subjects with diabetes should be individualized taking into account factors like risk of hypoglycemia, effect on body weight, side effects and costs among the different factors. Moreover, it will also have to be taken into account if the patient has a history of cardiovascular disease or HF.

Highlights

- The interaction between diabetes and heart failure is a clinical important entity independent of other causes of hear failure.
- Diagnosis of DCM is quite challenging since patients with DCM may remain asymptomatic for long time and they do not present until in the late stages of the disease so high clinical of suspicion and early diagnosis is very important.
- The pathophysiology of DCM is complex and multifactorial, with end result of myocardial fibrosis and cardiac remodeling.
- Currently, SGLT2-provides promises in management of heart failure patients along the wide spectrum of ejection fraction and weather diabetics or not.
- Future large outcome trials for treatment of DCM should address pathophysiological mechanisms of this unique disease.

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