

Diabetic Cardiomyopathy: Cause or Consequence of Diabetes Mellitus?

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Abstract

The pathogenesis of diabetic cardiomyopathy (DC) is not understood completely. DC is an important complication of longstanding diabetes that is associated with high mortality and morbidity rates, being its progression controlled by multiple factors. Within the mechanisms that have been proposed for DC are included metabolic and microvascular disorders, insulin resistance, myocardial fibrosis and cardiac autonomic dysfunction, among others.

It is suggested that chronic hyperglycemia play an important role in the development of DC although multiple complex mechanisms and interplay of many molecular and metabolic events within the myocardium they could be involved with the pathogenesis. Some of the metabolic disorders associated with diabetes are hyperlipidemia, hyperglycemia and inflammation, which promote the formation of reactive species of oxygen and nitrogen, or other free radicals that induce the increase of diabetic nephropathy and cardiomyopathy.

Several adaptive responses caused by the metabolic alterations mentioned, trigger cardiovascular disorders including heart failure. In this article, we review some of the animal models and molecular mechanisms potentially implicated

in the progression of DC. In this article, we review some of the animal models and molecular mechanisms potentially implicated in the progression of DC.

Keywords: Diabetic Cardiomyopathy; Diabetes Mellitus; Heart Disease; Ischemic Heart Disease

Abbreviations

CAD - Coronary artery disease

DC - Diabetic cardiomyopathy

HTA - Arterial hypertension

DM - Diabetes mellitus

IC - Heart failure incidence

CD - Cardiovascular disease

HF - Heart failure

LV - Left ventricle

EF - Ejection fraction

NIDC - Non-ischemic diabetic cardiomyopathy

AGEs - Advanced glycation end products

ECM - Extracellular matrix

STZ - Streptozotocin

1. Introduction

Diabetic cardiomyopathy (DC) is a pathological condition that increases morbidity and mortality rates associated with diabetes. In the underlying mechanisms of DC that lead to myocardial injury and cardiomyopathy, the hyperglycemia, hyperinsulinemia and oxidative stress play a relevant role in inducing, for example, the increase of advanced glycation end products (AGEs), inflammation, fibrosis, hypertrophy and apoptosis.

The Diabetes mellitus (DM) is considered a public health problem. The multiple complications associated with DM, increase the incidence, morbidity and mortality in diabetic patients, where heart disease is the leading cause of death.

It has been reported that one of the major causes of heart failure and death in diabetic patients (HF) is coronary artery disease (CAD). The risk of HF continues to increase despite adjustment for CAD and hypertension [1]. Rubler et al., Described DC as "a cardiac entity, defined as ventricular dysfunction in the absence of CAD and hypertension" [2]. At the clinical level, DC has been characterized by cardiac hypertrophy and diastolic dysfunction, which generally results in HF with preserved ejection fraction (HFpEF).

In some articles it is argued that DC can lead to systolic heart failure (HFrEF), although more evidence is needed to

support this finding [3]. By 2015 it is estimated that the diabetic population will be almost 300 million, due to an increase in obesity and physical inactivity.

50% of the deaths occurring in the diabetic population are due to cardiovascular disease (CD), causing an annual mortality twice that observed in non-diabetic population and a reduction in the life expectancy of 5-10 years. The cardiovascular damage caused by diabetes occurs at different levels, in epicardial arteries, autonomic malfunction, DC and microvascular coronary disease, being common the coexistence of multiple affections [4, 5].

In the diabetic patients one exists developing predominance, so much of HF as of malfunction ventricular (systolic, diastolic or mixed) asymptomatic not related with cardiovascular disease, hypertension, alcoholism, illness valve or congenital, so called entity “diabetic cardiomyopathy”, which it determines a prognosis typically of major adversity [6]. DM is a predictive indicator of cardiovascular mortality considering only ischemic patients.

Both the study SOLVD and the BEST not they demonstrated major mortality risk in diabetics with cardiomyopathy of origin not ischemic [7, 8]. Several epidemiological studies from the 1970s to 1979 support the high incidence of HF in DM, with a 2-fold risk in men and 5-fold in women, compared to the non-diabetic population matched by age and sex [4, 5].

2. Clinical Diabetic Cardiomyopathy

Although many studies on DC have been published and there is more clinical evidence, the debate on the existence of this pathology remains controversial, because DC does not have classic features of cardiomyopathy, such as ventricular dilatation and significant systolic dysfunction.

DC includes a connection of molecular myocardial abnormalities predisposing to myocardial dysfunction, particularly in the presence of additional stressors such as hypertension and CAD. [9]. The definition of diabetic cardiomyopathy (DC) is still discussed, since the CI in diabetic patients frequently collaborates with hypertension and CE, being difficult to unleash the myocardial damage caused by these two pathologies.

There are studies in which it is questioned that the DM by one is sufficient to explain the cardiomyopathy and only the myocardial one accepts the structural damage because of the diabetes associated with the AHT, which would take the ventricular malfunction as the first statement and in last Instance the IC [10]. Bell [11] states that if diabetes is not complicated by neuropathy, nephropathy, retinopathy, ETS or EC does not cause ventricular malfunction.

Nevertheless, when one associates not treated HTA and/or to ischemic myocardial the proper light subclinical cardiomyopathy of the diabetes can advance quickly to a diastolic malfunction clinically clearly and, more lately, to a malfunction systolic [11]. Pathologic changes in the myocardial interstitium, including AGE formation, impaired compliance and ischemia from the disease in the vasa vasorum, occur during the progression of DC.

These alterations lead to a deregulation of cardiac contractility, although the myocardial cells and coronary vessels maintain their morphological characteristics integrally [12]. When DC begins, LV hypertrophy occurs due to an enlargement of the cardiac cells, in addition to interstitial and perivascular fibrosis, thickening of the basement membrane of the capillaries and formation of microaneurysms in small capillary vessels [13].

The systemic proinflammatory state, with vascular inflammation and endothelial dysfunction, observed in diabetic patients also leads to the undesirable effects of LV hypertrophy and diastolic stiffening seen in DC. The endothelial dysfunction involving the coronary vasculature and central cardiac endothelium limits nitric oxide (NO) bioavailability to adjacent cardiomyocytes, decreasing cyclic guanosine monophosphate (cGMP) production and protein kinase G (PKG) activity in cardiomyocytes, culminating with the histological and functional alterations of DC [14].

Other pathogenic mechanisms are produced to impair cardiac function and promote cardiomyocyte injury in diabetes: impairment of calcium homeostasis, altered signal transduction (insulin signaling and renin-angiotensin system up regulation), altered cell homeostatic processes such as apoptosis and autophagy, changes in gene regulation (activation of transcription factors, microRNAs and epigenetic mechanisms), post-translational modifications of structural and signaling proteins, increased oxidative stress, cardiac autonomic neuropathy (CAN) and mitochondrial dysfunction [15-18].

When diabetic patients develop ventricular dysfunction in the absence of atherosclerosis and hypertension, the diagnosis may be focused towards a DC [18-22]. Despite this, DC can go unnoticed for a long time, before the appearance of clinical signs or symptoms [23]. In asymptomatic diabetic patients, cardiac abnormalities most frequently observed include diastolic cardiac dysfunction and left ventricular hypertrophy (LVH) [18, 24-26].

The progression of cardiomyopathy involves the onset of time-dependent heart muscle disease, which includes a subclinical period in which the symptoms and frequent signs of the disease are absent. Therefore, the most significant evidence to diagnose DC is the verification of ventricular malfunction in asymptomatic young diabetic patients, with no other concomitant pathologies capable of affecting the cardiac muscle, and in which myocardial anomalies are due exclusively to adequate diabetes.

Marcinkiewicz et al. [27] defined DC as the long-lasting process, which affects the myocardium, which is established, at a very early stage of metabolic changes (such as insulin resistance or overexpression of resistin), Even before diabetes is diagnosed. Its onset is accelerated by progressive myocardial ischemia [27].

In addition to cardiac malfunction related to ischemia, there are studies that show association between heart failure and diabetes in both type 1 and type 2 diabetes mellitus. The molecular and physiological mechanisms of non-ischemic diabetic cardiomyopathy (NIDC) are still unclear and the Studies on the mechanics of the myocardium in

the early stages of the disease are rare.

However, several studies in both humans and animal models have described the occurrence of early myocardial hyperdynamics during the course of the disease. The theory that emerges is that NIDC may be nonlinear and initially present an asymptomatic subclinical phase of myocardial hypercontractility that precedes the long-term development of cardiac dysfunction associated with diabetes and, ultimately, the HF [28].

Metabolic alterations induced by diabetes can lead to a contradictory inotropic increase and a mechanical deregulation of the myocardium that eventually result in a gradual deterioration of myocardial performance. Accordingly, diabetic patients should undergo periodic examinations during the course of the disease using, among others, ultra-sensitive images of myocardial deformation in order to identify patients at risk for heart failure associated with diabetes.

In addition, hyperdynamic myocardial deformation may improve the diagnosis of non-ischemic cardiomyopathy of ischemic diabetic cardiomyopathy. Further studies are needed to elucidate the underlying pathophysiological mechanisms as well as the spatiotemporal evolution of DC and its long-term relationship with clinical outcome parameters [28].

3. Pathogenesis of Diabetic Cardiomyopathy

The pathogenesis of DC is complex and has not been well understood until recently. Several mechanisms have been proposed, each of which acting lonely or in combination with the others, it can give place to the DC. The main ones are the following ones: metabolic illness, interstitial fibrosis, myocellular hypertrophy, microvascular illness and autonomic malfunction. Impaired calcium handling, altered metabolism, increased oxidative stress, remodeling of extracellular matrix (ECM), endothelial and mitochondrial dysfunction are some of the alterations involved in DC [29-32].

DM is pathology involved in HF, despite the absence of alterations in coronary artery disease, hypertension, left ventricle (LV) and ejection fraction (EF). This condition is known as diabetic cardiomyopathy [33-35]. Although the diagnosis of CD is believed to be multifactorial, the exact cause remains unknown. Several mechanisms, including hyperglycemia and hyperinsulinemia, play a relevant role in its etiology.

These alterations are observed as changes in free acid metabolism, increased apoptosis, activation of the renin-angiotensin system, abnormalities in copper metabolism, autonomic neuropathy, stem cell defect, and increased oxidative stress among others. The underlying pathological conditions may change cardiac structure and lead to cardiac fibrosis [33].

DC is a left ventricular diastolic dysfunction, identified in patients with DM as the earliest functional alteration in

the progression of diabetic cardiomyopathy [33-35], constituting an important prognostic parameter. In addition, LV longitudinal myocardial systolic dysfunction has been identified in patients with DM with preserved FEVES without evident coronary disease or HF [37].

Other investigators have found that LV myocardial systolic dysfunction, rather than LV diastolic dysfunction, could be considered as the first sign of a preclinical form of a preclinical form of DC in patients with DM with FEVES preserved without open IC [33-37]. In spite of this, the characteristics of the patients with DM that are associated with alteration of the longitudinal systolic myocardial function of the LV are still unclear.

4. Metabolic Illness

At cellular level, the DC associates with anomalies of the metabolism of the greasy acids and of the homeostasis of the calcium, what can produce major rigidity of left ventricular wall and deterioration of the contractility the cardiac cell [38].

Studies in animals have shown that diabetes induced experimentally produces defects in cellular calcium transport, defects in contractile proteins and increased production of collagen that causes small anatomical and physiological changes in the myocardium of monkeys [38-40]. In other studies it has been suggested that using more fatty acids associated with decreased glucose consumption leads to an accumulation of toxic intermediate fatty acids which subsequently inhibit this consumption of glucose into the myocardium.

This can derive a depletion of ATP, prevention in the production of lactate and increase in the oxygen consumption myocardial, quite which leads to a deterioration of the yield myocardial [41, 42].

5. Model Animals And Molecular Targets

In spite of the studies, the initial response of myocardial tissue to a short period of hyperglycemia in terms of proliferative properties of myocytes and alterations in the storage of cardiac stem cells is still to be investigated before the cardiomyopathic phenotype is evident.

A detailed knowledge of the changes that occur at the beginning of diabetes, when cardiac electromechanical performance remains normal, could serve to generate effective therapeutic strategies aimed at the prevention of mechanical dysfunction and arrhythmogenesis, which characterize the more advanced stages of DC. For the development of one animal model in rats for diabetes, intraperitoneal injection of streptozotocin (STZ, 60 mg/kg) is used in a single dose.

In this model, rats show hyperglycemia and hyperlipidemia together with hyperinsulinemia [44]. Ventricular dysfunction and marked structural damage occur over 12 weeks posttreatment with STZ. The first detrimental effect of metabolic changes is a marked loss of ventricular mass, with no signs of cardiomyocyte hypertrophy or

accumulation of extracellular matrix [23]. However, in STZ-injected rats, it is not possible to state that the symptoms presented in these animals are related, with a permanent toxic action of STZ [45, 46].

As has been reported, wild rodents are resistant to the development of CAD unless mutations are introduced that induce the development of atherosclerosis, making these animals a good model for the study of DC. [47-49]. In various rodent models for type 2 diabetes including db / db, ob / ob and Zucker diabetic obese rats, cardiac hypertrophy has been observed with increased LV wall mass and thickness, and diastolic dysfunction measured by echocardiography or RM [47, 49-52].

In these models systolic dysfunction is observed dependent on the degree of hyperglycemia and diabetes, confounded by echocardiography or ex vivo techniques such as heart perfusion of Langendorff or in the isolated heart model [51,53,54]. Several mechanisms have been described to demonstrate the development of diabetic cardiomyopathy, with other manifestations associated with heart failure, including, among others, oxidative stress, mitochondrial dysfunction, increased fibrosis, deterioration in calcium management, increased inflammation, increased Cell death and increased activation of the renin-angiotensin system [47].

The pathological alterations observed in cardiomyocytes are generally produced by systemic metabolic alterations such as hyperglycemia, hyper and dyslipidemia, hyperinsulinemia and insulin resistance. Increased myocardial fatty acid uptake and the generation of toxic lipid intermediates induce increased apoptosis, oxidative stress, and LV dysfunction. It is noteworthy that insulin resistance may contribute to mitochondrial dysfunction and decoupling, oxidative stress, cardiovascular inefficiency, and myocardial energy depletion [49,55-57].

Thus, in the rodent models for type 2 diabetes as in humans it has been possible to observe the occurrence of the DC, as well as associated diastolic dysfunction[47].

In STZ and Akita diabetic mice, diastolic dysfunction is characterized by increased LV diastolic pressure with cardiac catheterization and abnormal patterns of mitral and venous pulmonary flow [49, 58-60]. On the other hand, in systolic function, there is damage of the ejection fraction and cardiac dysfunction [57, 61].

In a reported study, the authors evaluated by magnetic resonance the early characteristics of DC, in STZ mice, one week after their inoculation observing early reduction of LV volumes which may be explained by hypovolemia due to hyperglycemic osmotic diuresis, inferring a hemodynamic mechanism contributing to cardiac dysfunction in this model of DC [49, 62].

In cardiomyocytes isolated from OVE26 mice, disruption of contractility has been observed, but not in heart perfusion [63, 64]. In Akita diabetic mice, both young and adult, systolic function is conserved both in vivo and ex vivo [65, 66]. In these mice, cardiac hypertrophy is not observed, but isolated hearts are smaller than in non-diabetic controls [66, 67].

This observation may be related to the lack of insulin's effect on cellular growth and protein synthesis, as also underlined by decreased cardiac size in mice lacking insulin receptors specifically in cardiomyocytes [49]. In the description of the underlying mechanisms of DC, but not in all the models studied nor for all the associated alterations, many observations seem to overlap with the alterations found in the hearts of type 2 diabetes.

Akita diabetic mice apparently do not develop fibrosis, no myocardial inflammation, oxidative stress or decreased cardiac efficiency are observed, although some typical features of DC, such as disruption in calcium management, mitochondrial dysfunction or increased use of Fatty acids [60, 64, 65]. Likewise, mice with STZ-induced type 1 diabetes do not exhibit decreased cardiac efficiency unless they develop insulin resistance, as observed in type 2 diabetic hearts, induced by insulin receptor deletion.

For STZ mice, it can not be ruled out that this drug may induce extrapancreatic toxic effects that may alter the cardiac phenotype [49, 66, 67]. Similarly in humans, in type 1 diabetic animals, insulin therapy can reverse phenotypes and abnormalities such as diastolic dysfunction, decreased expression of the sarcoendoplasmic reticulum Ca^{2+} -ATPase 2a (SERCA2a), mitochondrial dysfunction or oxidative stress [49, 60, 68].

According to the above, both the phenotype and the molecular mechanisms seem to be different, for the type 1 and 2 diabetes models studied. At the molecular level, several proteins and signaling pathways have been implicated in the development of DC, including protein kinase C, nuclear factor κ B, peroxisome proliferator-activated receptor, phosphatidylinositol 3 kinase (PI3K) And the MAPK pathway [32, 69, 70].

In this context, microRNAs (miRs or miRNAs) may be involved in the pathogenesis of DC, as these molecules have been associated with several biological processes, including cell proliferation, apoptosis, necrosis, migration and differentiation. Deregulation of these small RNAs may influence the progression and severity of diabetes and cardiovascular diseases [71-74].

For example, miR-126, miR-17, miR-92a, miR-145, miR-155, miR-133 and miR-208a were identified to be associated with coronary artery disease; miR-1, miR-21, miR-208, miR-133a/b, miR-499 were identified as important in the diagnosis of acute cardiac infarction. Furthermore, miR-24, miR-125b, miR-195, miR-199a and miR-214 were associated with heart failure [32, 74-76].

Huo et al. [77], produced a model of DC rats in which the expression of the long non-coding RNA H19 is decreased. Other authors studied the role of H19 in DC and showed that overexpression of H19 in diabetic rats decreases autophagy of cardiomyocytes and improves LV function. In addition, they reported that high glucose levels reduced H19 expression and increased autophagy in neonatal cardiomyocyte cell cultures.

Immunoprecipitation of RNA-binding and chromatin (ChIP) binding proteins showed that H19 can bind directly to

EZH2 in cardiomyocytes and that the decrease in H19 expression may inhibit the binding of EZH2 and the formation of complexes of H3K27me3 in the promoter Of DIRAS3. On the other hand, it was demonstrated that H19 overexpression decreases the expression of DIRAS3, promotes mTOR phosphorylation and inhibits the activation of autophagy in cardiomyocytes exposed to high glucose levels, which in turn induces increased expression of DIRAS3 as well As of autophagy by inhibiting mTOR signaling in cardiomyocytes. These studies show that H19 inhibit autophagy by epigenetic silencing de DIRAs 3 in cardiomyocytes, which might provide novel insights into understanding the molecular mechanisms of DC [77].

On the other hand, SIRT1 is a nicotinamide adenosine dinucleotide (NAD)-dependent deacetylase that removes acetyl groups from proteins which can be implicated in DCP.

SIRT1 regulates the expression of several proteins related to hyperglycemia and inhibits the expression of transcriptional factors, such as p300, NF- κ B, P38MAPK, Histone 3, MMP-9, FOXO3a and p53. Additionally, SRT1 induces the increase in the expression of, SERCA2a, ERK1 /2/Homer1, eNOS, PGC-1 and AMPK, therefore, this gene, decreases cardiac dysfunction and improve DC [78].

6. Conclusion

The DC is a pathological condition that increases morbidity and mortality rates associated with structural, functional and metabolic changes. As the mechanisms involved in the pathogenesis of DC continue to be elucidated, it is necessary the study the risk factors in patients with DC as well as the animal models and target molecules that can generate knowledge to create more specific and effective therapies for the patients with this pathology. From this perspective, is diabetic cardiomyopathy a cause or consequence of diabetes mellitus?

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Author Contributions

All authors contributed to the writing of this review.

Conflicts of Interest

The authors declare no conflict of interest.

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