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Present Insights on Cardiomyopathy in Diabetic Patients

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Abstract: The pathogenesis of diabetic cardiomyopathy (DCM) is partially understood and is likely to be multifactorial, involving metabolic disturbances, hypertension and cardiovascular autonomic neuropathy (CAN). Therefore, an important need remains to further delineate the basic mechanisms of diabetic cardiomyopathy and to apply them to daily clinical practice. We attempt to detail some of these underlying mechanisms, focusing in the clinical features and management. The novelty of this review is the role of CAN and reduction of blood pressure descent during sleep in the development of DCM. Evidence has suggested that CAN might precede left ventricular hypertrophy and diastolic dysfunction in normotensive patients with type 2 diabetes, serving as an early marker for the evaluation of preclinical cardiac abnormalities. Additionally, a prospective study demonstrated that an elevation of nocturnal systolic blood pressure and a loss of nocturnal blood pressure fall might precede the onset of abnormal albuminuria and cardiovascular events in hypertensive normoalbuminuric patients with type 2 diabetes. Therefore, existing microalbuminuria could imply the presence of myocardium abnormalities. Considering that DCM could be asymptomatic for a long period and progress to irreversible cardiac damage, early recognition and treatment of the preclinical cardiac abnormalities are essential to avoid severe cardiovascular outcomes. In this sense, we recommend that all type 2 diabetic patients, especially those with microalbuminuria, should be regularly submitted to CAN tests, Ambulatory Blood Pressure Monitoring and echocardiography, and treated for any abnormalities in these tests in the attempt of reducing cardiovascular morbidity and mortality.

Keywords: Diabetic cardiomyopathy, diabetes mellitus, left ventricular hypertrophy, left ventricular dysfunction, ambulatorial blood pressure measurement, diabetic autonomic neuropathy.

INTRODUCTION

Patients with diabetes mellitus (DM) are at increased risk for cardiovascular diseases, which are the leading cause of diabetes-related morbidity and mortality [1]. DM has multifactorial detrimental effects on myocardial tissue [2] and is commonly associated with hypertension and coronary atherosclerosis [3], increasing the risk for myocardial infarction, stroke and limb loss [4]. Furthermore, some clinical, epidemiological and histopathological data support the occurrence of a specific cardiomyopathy related to diabetes, independent of additional cardiovascular risk factors, a condition known as diabetic cardiomyopathy (DCM). It has been defined as "a distinct entity characterized by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease (CAD), hypertension, and significant valvular disease" [5-6]. Therefore, the concept of diabetic cardiomyopathy is based on the notion that diabetes itself is the key factor eliciting changes at the molecular and cellular levels of the myocyte, culminating in structural and functional abnormalities in the heart [7].

The existence of DCM was first suggested by Rubler *et al.* [7], in 1972, on the basis of autopsy findings in four diabetic adults with congestive heart failure in the absence of coronary, valvular, congenital and hypertensive heart disease. In 1977, Regan *et al.* [8] provided more definitive evidence for this newly recognized condition. After ruling out large and small vessel disease by coronary angiography and the absence of lactate production during atrial pacing, respectively, four adult diabetic patients were found to have left ventricular (LV) dysfunction, presenting increased LV-end-diastolic pressure, normal LV-end-diastolic volume, decreased LV compliance and, in three of them, low ejection fraction with diffuse hypokinesis. In addition, the role of DM as a causal factor in the development of congestive heart failure was more conclusively delineated in the Framingham Heart Study, which found this condition to be more frequent in diabetic patients when compared to age-matched control subjects, independently of age, weight, office blood pressure, hypercholesterolemia and coronary artery disease [9]. Studies using independent population databases have provided similar results, revealing increased heart failure rates in subjects with diabetes mellitus in cross-sectional analyses and

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increased risk for developing heart failure in prospective analyses, even after correction for confounding variables [10-12].

The natural history of diabetic cardiomyopathy ranges from a short-term physiological adaptation to the metabolic alterations of diabetes through to degenerative changes which the myocardium is unable to repair, ultimately culminating in irreversible pathological remodeling [13]. Clinically, the spectrum of myocardial dysfunction in DCM involves a progression from the normal heart to subclinical cardiac abnormalities (LV diastolic and systolic dysfunction and LV hypertrophy), that must be evaluated carefully during detailed imaging techniques (echocardiography). Finally, symptomatic heart disease develops [14-15]. We and others have found that, in diabetic patients, subclinical cardiac abnormalities, when early detected, could be reversible [16-21].

The percentage of patients with diabetes and heart failure was up to 26% in the Studies of Left Ventricular Dysfunction (SOLVD) [22], 19% in the Assessment Trial of Lisinopril and Survival (ATLAS) study [23], and 20% in the Vasodilator-Heart Failure Trial II (V-HeFT II) [24]. Although proven to be a highly prevalent and important condition, diabetic cardiomyopathy is still poorly recognized by most clinicians and epidemiologists [25], and its etiology is still far from being fully elucidated [26].

The pathogenesis of diabetic cardiomyopathy is likely to be multifactorial, involving complex cellular and molecular perturbations that predispose to altered myocardial structure and function. Despite the current knowledge on diabetic cardiomyopathy, translational research is lacking due to limited human myocardial tissue, and most of the scientific data on this condition is gained and extrapolated from experimental studies [26].

Some appealing hypotheses to explain the development of DCM have been proposed, and are centered on metabolic disturbances (such as hyperglycemia, increased circulating fatty acids and triacylglycerols, hyperinsulinemia and increased inflammatory cytokines), which alter multiple molecular pathways within the cardiomyocyte, as well as every cellular element within the vascular walls, leading to impaired cardiac contractility and promoting myocyte dysfunction, injury and cell apoptosis [27-29].

The early stages of DCM are dominated by the pathological alterations in the myocardial interstitium, including the formation of nonenzymatic advanced glycation end products (AGEs), impaired compliance, and ischemia from the disease in the *vasa vasorum*. These alterations lead to impaired myocardial contractility, despite the anatomically preserved morphology of the myocardial cells and small coronary vessels [30]. As the disease progresses, LV hypertrophy appears as a result of the hypertrophy of the myocardial cells, the interstitial and perivascular fibrosis, the greater thickening of the capillary basement membrane, and the formation of microaneurysms in small capillary vessels [31].

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 DCM. 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 DCM [32].

Other pathogenic mechanisms act in concert to impair cardiac function and promote cardiomyocyte injury in diabetes: impaired 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, mitochondrial dysfunction and cardiac autonomic neuropathy (CAN) [4, 27, 29, 33].

In summary, many potential mechanisms have been proposed and studied, but some of them remain relatively underinvestigated and require further study. Therefore, an important need remains to further delineate the basic mechanisms of diabetic cardiomyopathy and to apply them to daily clinical practice. In the following sections, we attempt to detail some of these underlying mechanisms, focusing in the clinical features and management.

CARDIAC PRECLINICAL DAMAGE

Diabetic cardiomyopathy is a distinct entity diagnosed when ventricular dysfunction develops in patients with diabetes in the absence of coronary atherosclerosis and hypertension [34-37]. However, DCM may be subclinical for a long time, before the appearance of clinical signs or symptoms [38]. The most commonly observed cardiac abnormalities in clinical studies of asymptomatic diabetics include diastolic cardiac dysfunction and left ventricular hypertrophy (LVH), which configure preclinical abnormalities [10, 39-40].

Diastolic Dysfunction

Left ventricle diastolic dysfunction is a major characteristic of DCM [41] and has been described as the initial functional alteration in the diabetic myocardium [29]. It is determined by a delayed and extended diastolic phase, with impaired early diastolic filling, prolongation of isovolumetric relaxation, increased atrial filling and increased myocardial stiffness, predominantly in late diastole [28, 42-43]. Electrophysiologically, diastolic dysfunction is characterized by the prolongation of the active dilatation and the augmented passive stiffness of the left ventricle, which portray the passive diastolic LV compliance in heart failure [44].

Impaired diastolic functioning of the left ventricle has been largely demonstrated in diabetic patients without clinically detectable heart disease [45-48]. Using conventional echocardiography and tissue Doppler imaging, it can be detected in 40 to 75% of patients with type 1 or type 2 diabetes [49-50]. From *et al.* [51] performed a tissue Doppler echocardiographic assessment of diastolic function in a large community-based cohort of 1760 diabetic patients. A high

prevalence of asymptomatic LV diastolic dysfunction was found and it was associated with the subsequent development of heart failure and increased mortality independent of hypertension, coronary disease, or other echocardiographic parameters. Additionally, Van Heerebeek *et al.* [52] compared LV endomyocardial biopsy samples of diabetic and non-diabetic patients with heart failure with preserved ejection fraction (HFpEF), all without coronary artery disease. Diabetic heart failure patients presented higher LV diastolic stiffness, irrespective of LV ejection fraction, which was predominantly attributed to augmented cardiomyocyte resting tension. Further evidence comparing HFpEF patients with and without DM showed that diabetic HFpEF patients had reduced exercise capacity and increased risk of hospitalization, associated with a more severe disease phenotype characterized by greater LV hypertrophy, and elevated circulating markers of oxidative stress, inflammation and fibrosis [53].

Furthermore, changes in diastolic function have also been widely reported in diabetic animals without evidence of heart disease caused by other factors [54-57]. Research on rodent models of type 1 and type 2 diabetes, and the use of genetic engineering techniques in mice have greatly advanced the understanding of the molecular mechanisms responsible for human diabetic cardiomyopathy [58]. Studies with both *db/db* and streptozotocin-diabetic mice have suggested that an increased fatty acid uptake and altered intracellular calcium handling in cardiomyocytes might be involved in contractile dysfunction [59-61].

Left Ventricular Hypertrophy

In addition to diastolic dysfunction, DCM is characterized by a disproportionate increase in LV mass and myocardial fibrosis. LV mass indexes (LVMIs) above 125 g/m^2 in men and above 110 g/m^2 in women configure left ventricular hypertrophy [28]. Echocardiographic changes consistent with LVH have been described in a number of studies of diabetic populations and may portend an increased risk for the subsequent development of heart failure, particularly in the presence of coexisting hypertension [62-66]. In the Framingham Heart study, diabetic women had a LVMI 10% greater than the nondiabetic patients [66]. Furthermore, we have found that diabetic patients, when compared with nondiabetic individuals, presented a higher prevalence of LVH and diastolic dysfunction [67]. Additionally, it was demonstrated that the relative risk for cardiovascular mortality for each 50 g/m^2 increase of the LV mass above the normal limits was equal to 1.49 for men and 1.57 for women [68].

Several molecular and metabolic mechanisms have been linked to the development of LVH, such as hyperinsulinemia, insulin resistance, increased non-esterified fatty acids, higher circulating levels of leptin, activation of the renin–angiotensin system and increased reactive oxygen species [69]. Moreover, LVH is significantly associated with increased markers of systemic inflammation, such as fibrinogen, C-reactive protein, and microalbuminuria. Palmieri *et al.* [70], studying 1,299 patients with type 2 diabetes, found microalbuminuria to be associated not only with endothelial dysfunction and increased risk of atherosclerosis, but also with LV mass.

Systolic Dysfunction

As DCM insidiously progresses, with continuous eccentric cardiac remodeling [71], systolic dysfunction may also develop, usually following diastolic dysfunction [4, 6]. However, Ernande *et al.* [72], using systolic strain analyses, have recently found systolic dysfunction in diabetic patients with normal diastolic function, suggesting that diastolic dysfunction may not necessarily be the first functional alteration in diabetic cardiomyopathy.

Systolic dysfunction can lead to congestive heart failure and sudden death [6, 38]. In later stages, when clinically established, it may be accompanied by bradycardia, reduced systolic blood pressure and fractional shortening [6]. The prognosis of patients with LV systolic myocardial dysfunction is poor, and the percentage of annual mortality is equal to 15%–20% [28].

Diagnosis of Subclinical Heart Disease

The diagnosis of DCM stems from the detection of myocardial abnormalities and the exclusion of other contributory causes of cardiomyopathy. Diastolic myocardial function can be detected by cardiac catheterization, evaluating the LV isovolumetric relaxation rhythm and contraction time [73]. However, this method, although highly accurate, is invasive and has increased possibilities of accidental injury [28]. Therefore, in clinical practice, the diagnosis of DCM rests on non-invasive imaging techniques that can demonstrate myocardial dysfunction across the spectra of clinical presentation [27].

Conventional echocardiographic approaches, such as two dimensional (2D) echocardiography, are reliable for the determination of LV hypertrophy and both systolic and diastolic dysfunction in patients with established structural changes in the cardiomyocytes [28, 74]. However, since the initial stage of DCM might be disguised by various compensatory mechanisms [74], standard echocardiography testing fails to detect mild and early diastolic dysfunction in approximately one-third of subjects with normal arterial blood pressure levels [43, 46, 75]. Therefore, using conventional echocardiography, subtle diastolic and systolic dysfunction may configure a diagnostic challenge [29].

In addition, the diastolic function echocardiographic parameters (peak flow velocity of early left ventricular filling, peak flow velocity of late left ventricular filling, early deceleration time, isovolumetric relaxation period and the ratio between early and late diastolic flow velocity peaks), although useful in population studies, present significant individual variability. Moreover, despite the excellent reliability of echocardiography for measurement of left ventricular mass (intraclass coefficient of correlation 0.86), the 95% confidence interval (CI) width of a single replicate measurement of left ventricular mass is 59 grams, exceeding usual decreases in mass during treatment. However, within a population, the CI decreases proportionally with the inverse of the square root of the sample size, which makes it possible to evaluate decreases and increases in LVMI in large groups [76].

Therefore, the substructural changes in the cardiomyocytes observed in the early stages of DCM can only be de-

tected by more advanced and sensitive methods of cardiac evaluation, such as Doppler myocardial imaging (strain, strain rate and myocardial tissue velocity) [6, 77-78]. Recent studies using these techniques revealed that over 50% of cardiovascular asymptomatic diabetic patients present diastolic dysfunction [6, 45-46, 79-81]. Similarly, using strain analysis and measurements of peak systolic velocity, subtle abnormalities in systolic function have been described in 24% of patients with diabetes mellitus without CAD or LV hypertrophy [82]. A wider use of these newer techniques is extremely important to a better evaluation of both diastolic and systolic function in DCM.

Additionally, cardiac magnetic resonance imaging (MRI) is a very promising imaging tool for the diagnosis of various structural and functional cardiac disorders [83-84], including diastolic dysfunction and myocardial steatosis [85]. Furthermore, Kwong *et al.* [86] suggested that gadolinium-enhanced cardiac MRI might be useful to predict major adverse cardiac events, such as acute myocardial infarction, development of heart failure and ventricular arrhythmias in diabetic patients without previous history of ischemic heart disease. Moreover, cardiac MRI using different radionuclides and positron emission tomography (PET) can also detect myocardial metabolic abnormalities [25]. However, considering the expenses, these methods still do not apply to daily clinical practice.

In addition to imaging techniques, the role of diagnostic biomarkers has been discussed for the early detection and development of novel therapeutic implications of diabetes-associated cardiovascular complications. In the attempt to diagnose the disease at molecular level, various biomarkers have been studied [87-88]. MicroRNAs (miRs) have recently been implicated in cardiovascular events through the regulation of cardiac gene expression, and are also released in to the circulation in disease states, serving as potential diagnostic biomarkers for cardiovascular disease. Therefore, modulated levels of these circulating cardiovascular miRs before the clinical manifestation of heart disease augment the opportunities to provide new clues for early detection of this condition in diabetic subjects, for disease prognosis and for assessing the efficacy of therapeutic interventions. However, those biomarkers are not available yet for clinical practice [88].

ROLE OF HYPERGLYCEMIA

It has been suggested that hyperglycemia is one of the main responsible for the damage caused by diabetes on the cardiac myocytes, eventually leading to the structural and functional abnormalities of DCM [38, 89-90]. The severity and duration of hyperglycemia has been shown to directly parallel the incidence of diabetic cardiomyopathy in patients with diabetes [91].

Hyperglycemia may contribute to DCM through multiple mechanisms. Barbagallo *et al.* [89] performed a multivariate regression, which indicated that the contribution of glucose levels to LVMI was independent of age, body mass index, fasting insulin levels and blood pressure, and demonstrated a significant interaction with intracellular calcium. Altogether, these data suggest that glucose-related excess intracellular calcium is a fundamental lesion in diabetes that contributes to the elevated blood pressure and cardiac mass in this disease.

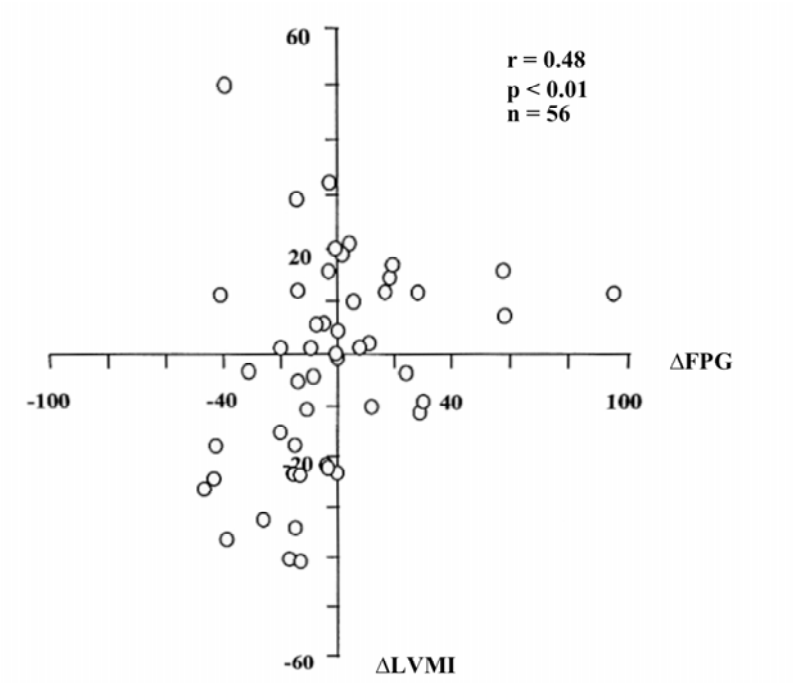
Furthermore, sustained hyperglycemia may increase glycation of interstitial proteins such as collagen, resulting in myocardial stiffness and impaired contractility [92-94]. The myocardial content of free radicals and oxidants is also increased by high blood glucose levels, which leads to decreased nitric oxide levels, worse endothelial function, and induces myocardial inflammation through stimulation of poly(ADP-ribose) polymerase-1 [95]. Moreover, reactive oxygen species derived from high levels of glucose have been directly associated with myocyte apoptosis and necrosis, which may impair myocardium contractility [96].

Additionally, increasing evidence demonstrates that AGEs play a pivotal role in the development and progression of diabetic heart failure. AGEs are generated intra- and extracellularly as a result of chronic hyperglycemia, and once formed, they are irreversible. Then, following the interaction with receptors for advanced glycation end products (RAGEs), a series of events leading to vascular and myocardial damage are elicited and sustained, which include increased inflammation, and enhanced extracellular matrix accumulation resulting in diastolic and systolic dysfunction [97-99]. Furthermore, AGEs generate toxic reactive oxygen species that impair cellular interactions and damage myocardial vascular function, causing endothelial vasomotor dysfunction [100].

Some multicenter prospective studies have shown a strong relationship between glycemic control and cardiovascular disease in individuals with DM. The Diabetes Conventional and Complications Trial (DCCT) showed that patients with diabetes who are conventionally treated have a nearly double incidence of cardiovascular disease when compared with patients with diabetes who are intensively treated [101]. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a 14% reduction in myocardial infarction for each 1% reduction in HbA1c [102]. In addition, data from the Strong Heart Study revealed that DM participants with abnormal LV diastolic filling had higher levels of HbA1c and fasting glucose than DM individuals with normal LV diastolic function [104]. However, the benefit of an intensive glycemic control has not been proven definitive for patients with DCM, especially those with associated macrovascular diseases.

Moreover, it has been demonstrated that the association between DM and LV diastolic dysfunction is not limited to established or advanced DM, but also exists along the entire spectrum of glucose metabolism, including pre-diabetes, suggesting that even mild hyperglycemia may contribute to DCM [104-105]. These findings support a relevant role for early preventive measures to improve glucose metabolism on a population scale, which are especially critical in preclinical diastolic dysfunction, as no effective treatment has been identified to date for diastolic heart failure once established [32, 104].

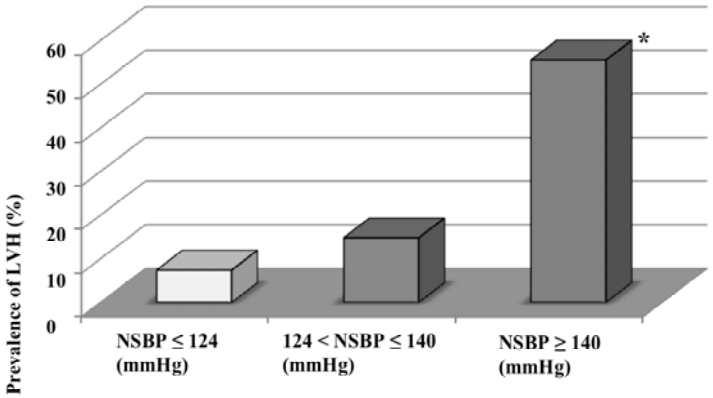
We were the first ones to demonstrate, in 2000, that the improvement of glycemic control in type 2 diabetic patients per se is capable of reverting left ventricular hypertrophy. The reduction of 10% in LVMI was associated with a fasting



FPG: Fasting plasma glucose

LVMI: Left ventricle mass index

Fig. (1). Correlation between blood glucose and LVMI percent variations (Δ) in patients with Type 2 DM.



*p<0.05 *versus* both other groups.
NSBP: Nocturnal systolic blood pressure.
LVH: Left ventricular hypertrophy.

Fig. (2). Nocturnal systolic blood pressure and left ventricular hypertrophy in patients with Type 2 DM and hypertension.

blood glucose reduction and a correlation was observed between blood glucose and LVMI percent variations (Fig. **1**). These results occurred independently of blood pressure and cholesterol levels, in diabetics without coronary artery disease. However, we didn't perform Ambulatory Blood Pressure Monitoring (ABPM) in these patients. The better glycemic control could be responsible for a reduction of nocturnal blood pressure levels, which could explain the improvement of the left ventricular mass index. Thus, the glycemic control would have an indirect effect on the left ventricular hypertrophy [16]. In addition, diabetic patients with nocturnal systolic blood pressure (NSBP) greater than 140 mmHg and elevated fasting blood glucose levels showed an additional risk for LVH (Fig. **2**) [67].

A few short-term studies have shown that LV hypertrophy, and diastolic and systolic dysfunction may improve with better glycemic control [16-21], as presented on Table **1**. Additionally, it has been demonstrated that failure to achieve glycemic control (decompensation) leads to deterioration in structural parameters of myocardial function [106-

Table 1. Data on the effect of a better glycemic control on the preclinical cardiac abnormalities of DCM.

Author (Publication Year)	Country	Type of Diabetes	Number of Patients	Parameters Improved with Fasting Blood Glucose and/or HbA1c Reduction
Felício *et al*. [16] (2000)	Brazil	Type 2	56	Reduction of LVMI.
Uusitupa *et al.* [17] (1983)	Finland	Type 2	33	Decrease of heart rate corrected PEP, increase of heart rate corrected LVET and decrease of PEP/LVET ratio.
Mustonen *et al.* [18] (1988)	Finland	Type 2	9	Decrease of PEP/LVET ratio.
Aepfelbacher *et al.* [19] (2004)	United States	Type 1	19	Regression of interventricular septal thickness and left ventricular mass.
Bibra *et al.* [20] (2004)	Sweden	Type 1	25	Decrease of diastolic resting velocity.
Grandi *et al.* [21] (2006)	Italy	Type 1	36	Improvement of diastolic parameters.

LVMI: Left ventricle mass index
PEP: Pre-ejection period
LVET: LV ejection time

108]. Furthermore, a recent review on diabetes and cardiovascular disease showed the role of an intensive glycemic control in the reduction of mortality rates and risk of complications after an acute myocardial infarction or cardiac surgery in diabetic patients [109]. These clinical data sustain the fact that glucose levels are critical to myocardial damage in diabetic patients; however, the mechanism responsible for this injury is not completely elucidated yet.

ROLE OF DYSLIPIDEMIA AND OBESITY

Dyslipidemia has been associated with worse myocardial performance in patients with type 2 DM [110], and various clinical studies have reported a significant decrease of cardiovascular risk in type 2 DM patients who undergo intensive lipidemic control [111-113]. Additionally, some studies have demonstrated an association between increased myocardial triglyceride content (myocardial steatosis) and systolic and/or diastolic dysfunction in diabetic patients [85, 114-115].

Hyperlipidemia may lead to fatty acids (FA) accumulation and lipotoxicity in the diabetic heart [116], affecting myocardial contractility and promoting cardiomyocyte cell death [91]. Excessive FA delivery and uptake by cardiomyocytes may exceed mitochondrial oxidative capacity, leading to the deposition of triacylglycerols and ceramides, resulting in cardiomyocyte steatosis and hypertrophy [25, 116]. Moreover, central obesity, in addition to increasing FA production, contributing to insulin resistance and atherogenesis, has also been independently associated with LV dysfunction [117-118]. Therefore, restoring cardiac energy metabolism, by correcting the imbalance between lipids and glucose as fuel substrates, might be a potential therapeutic strategy in the management of DCM [116].

In addition to the conventional treatment for dyslipidemia, the genetic manipulation of molecules involved in the initial steps of lipid absorption and accumulation has revealed cardioprotective properties and suggested potential strategies against DCM [119-121]. From this group, FAT/CD36 is the most studied molecule and currently has aroused the highest expectations due to its crucial role in lipotoxicity [122]. In order to determine the best treatment option, it becomes a clinical priority to recognize the stages and pathogenic factors of DCM in each diabetic patient.

ROLE OF HYPERTENSION

Hypertension commonly coexists with diabetes. In the United States, it was found in approximately 30% of patients with type 1 DM in 50% to 80% of patients with type 2 DM [123]. In diabetic subjects with DCM, the prevalence of hypertension is even higher [124]. Hypertension shares similar pathogenetic pathways with DCM, such as dyslipidemia, insulin resistance and hyperinsulinemia, accelerating the functional underlying process [28]. Left ventricular hypertrophy and cardiac diastolic dysfunction are more frequent and more likely to become clinically apparent in diabetic patients when associated with hypertension, suggesting a maximization of damage on the myocardium in the presence of both DM and hypertension [30, 125].

Cardiac dysfunction was shown to be worsened by hypertension in animal models of DCM [126], and in the Strong Heart Study the combination of DM and hypertension had more LV diastolic dysfunction than groups with either condition alone [103]. Additionally, Grossman *et al.* [127] showed that hypertensive patients with DM, when compared to essential hypertensive patients, had a higher LVMI independent of office blood pressure. However, this study did not

evaluate the blood pressure rhythm in 24 hours. Studying 91 hypertensive patients with type 2 DM, 59 nondiabetic hypertensive patients and 26 healthy control subjects with ABPM and echocardiography with Doppler, we demonstrated that diabetic patients presented higher NSBP and increased LVMI. These findings occurred independently of sex, age, body mass index and diurnal blood pressure levels. Patients with DM also presented a worse diastolic function (early deceleration time and peak flow velocity of late left ventricular filling) when compared to nondiabetic hypertensive patients [67].

ROLE OF DIABETIC AUTONOMIC NEUROPATHY AND ABSENCE OR REDUCTION OF BLOOD PRESSURE DESCENT DURING SLEEP

Diabetic autonomic neuropathy (AN) may also play a role in the development of DCM. Characterized by denervation and alterations in myocardial catecholamine levels, it has been associated with a high cardiac mortality rate [128-129] and constitutes an independent risk factor for silent myocardial ischemia [130-131].

CAN affects blood flow in the coronary vasculature and impairs the contractile function of the myocardium. Due to abnormal sympathetic tone, patients with CAN also present a reduction in the vascular elasticity and an increase of peripheral vascular resistance [132]. In addition, DCM has been linked to parasympathetic nervous dysfunction, confirmed by an important decrease of heart rate variability during deep breathing maneuver in subjects with type 1 DM and by the presence of pathological echocardiographic findings of the LV filling rhythm [133].

Furthermore, CAN has been associated with a reduction in the cardiac ejection fraction, impairment of systolic function and decreased diastolic filling, thus having an important contribution to the deterioration of diastolic myocardial function and DCM [134-137]. Correlation between the severity of CAN and the prevalence of diastolic dysfunction also has been demonstrated [138]. The presence of CAN seems to have an additive effect on the impairment in cardiac diastolic function (CDF) in patients with diabetes [136] and might serve as an early marker for the evaluation of LV diastolic dysfunction [134].

In early stages, CAN may be completely asymptomatic and detected by changes in heart rate variability and abnormal cardiovascular reflex tests (R-R response to deep breathing, standing and Valsalva maneuver). Advanced disease may be indicated by resting tachycardia (>100 bpm) and orthostasis (a fall in systolic boold pressure >20 mmHg or diastolic blood pressure of at least 10 mmHg upon standing without an appropriate heart rate response). The standard cardiovascular reflex testing, especially the deep breathing test, is noninvasive, easy to perform, reliable, reproducible and has prognostic value [139].

The main determinant of the blood pressure circadian pattern appears to be the sympathetic nervous system and increased nocturnal blood pressure has been described in diabetic autonomic neuropathy [140-142]. CAN could reduce nocturnal decline of blood pressure by reducing vagal tone and consequently increasing cardiac output during sleep [140, 143-144], which has been associated with a higher risk of cardiovascular complications [145-146].

ABPM can be particularly useful in detecting absence or reduction of blood pressure descent during sleep [147]. We assessed the reproducibility of ABPM measurements and the placebo effect on ABPM to determine its degree of reliability as to the measurement of pressure levels in patients with type 2 DM and hypertension. The results of our study showed that mean pressure values assessed by ambulatory blood pressure monitoring presented good reproducibility and were not affected by placebo [148]. These findings are similar to few data found in the literature [149-150].

DM has been associated with elevated levels of nocturnal blood pressure [140]. It has been suggested that poor metabolic control could be the mechanism responsible for this elevation [151]. Hyperglycemia modifies circulating plasma volume, which can interfere in renal hemodynamics and distribution of blood flow, altering the normal nocturnal blood pressure. In addition, insulin has a role in regulating the autonomic nervous system [152]. Ferreira *et al.* [153] demonstrated that an improved glycemic control in patients with type 1 DM was associated with decreased ABPM pressure averages and increased blood pressure fall overnight.

We have demonstrated a correlation of AN tests with LVMI and CDF in normotensive patients with DM2. Positive AN tests occurred even before LVH, impaired CDF and diabetic AN symptoms were present. This correlation was not found in the control group. Additionally, in diabetic individuals, AN tests were correlated with average glycated hemoglobin. Our data suggested that AN could precede LVH and be a contributing factor to preclinical cardiac abnormalities in normotensive patients with DM2. Thus, we recommend that AN tests should be regularly performed in patients with DM2, and that any abnormalities in those tests should be followed by a detailed cardiac evaluation [154]. These data reinforce the hypothesis that AN could be a via through which hyperglycemia could increase nocturnal blood pressure and lead to diabetic cardiomyopathy.

DIABETIC NEPHROPATHY AND DIABETIC CARDIOMYOPATHY

It is well known that diabetic patients with microvascular complications show the strongest association between diabetes and cardiomyopathy [91]. Accordingly, we have demonstrated that the absence or reduction of blood pressure descent during sleep is also associated with other microvascular complications in patients with type 2 DM, such as diabetic retinopathy and nephropathy. Our study showed that diabetic patients with retinopathy had higher NSBP levels than diabetic patients without retinopathy, independent of diurnal blood pressure, age, sex, duration of DM and body mass index. This result was confirmed by multivariate regression analysis, in which NSBP was an independent predictor of diabetic retinopathy [155].

In regard to diabetic nephropathy, we demonstrated in a prospective study that an elevation of nocturnal systolic blood pressure and a loss of nocturnal blood pressure fall might precede the onset of abnormal albuminuria and cardiovascular events in hypertensive normoalbuminuric pa-

tients with type 2 diabetes [156]. Additionally, the Strong Heart Study [157] showed that the degree of diastolic dysfunction was proportional to the level of microalbuminuria, even after adjusting for age, sex, BMI, systolic blood pressure, duration of diabetes, left ventricular mass, and presence of coronary artery disease. Furthermore, the Heart Outcomes Prevention Evaluation (HOPE) [158] study showed that the presence of microalbuminuria was associated with significant risk for congestive heart failure. Suggested mechanisms linking renal and cardiovascular disease include endothelial dysfunction, abnormalities of the renin–angiotensin system, and widespread vascular basement membrane defects [28]. Therefore, existing microalbuminuria could imply the presence of myocardium abnormalities, leading to increased ventricular scarring and stiffness [125]. Based on these findings, the detection of microalbuminuria has been suggested as a prescreening test for asymptomatic DCM, followed by echocardiographic screening [43].

CONCLUSION

Although the pathogenesis of DCM has not been completely elucidated yet, we consider the presence of CAN and reduction of blood pressure descent during sleep to play a pivotal role in the development of this condition. Evidence has suggested that CAN might precede left ventricular hypertrophy and diastolic dysfunction in normotensive patients with type 2 diabetes, serving as an early marker for the evaluation of preclinical cardiac abnormalities. Additionally, a prospective study demonstrated that an elevation of nocturnal systolic blood pressure and a loss of nocturnal blood pressure fall might precede the onset of abnormal albuminuria and cardiovascular events in hypertensive normoalbuminuric patients with type 2 diabetes.

Therefore, screening for DCM at the earliest and asymptomatic stage of development may allow earlier intervention and possibly reversion of LV dysfunction and LVH, preventing the progression to severe cardiovascular outcomes. We suggest that all type 2 diabetic patients, especially those with microalbuminuria, should be evaluated by ABPM and echocardiography to identify loss of nocturnal blood pressure fall and preclinical cardiac abnormalities (cardiac diastolic dysfunction and LVH), respectively. Once identified these conditions, an intensive control of 24-hour blood pressure (especially during the night), hyperglycemia and dyslipidemia must be achieved. This approach could have a significant impact in the prevention of diabetic cardiomyopathy and reduce cardiovascular morbidity and mortality in these patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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