BALNEO RESEARCH JOURNAL
English Edition
eISSN 2069-7619 pISSN 2069-7597 ROMANIAN ASSOCIATION OF BALNEOLOGY

Left ventricular diastolic dysfunction in diabetes mellitus and the therapeutic role of exercise training

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Balneo Research Journal DOI: http://dx.doi.org/10.12680/balneo.2019.254 Vol.10, No.2, May 2019 p: 145–152

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Abstract

Left ventricular diastolic dysfunction (LVDD) with normal ejection fraction is considered common among people with diabetes mellitus (DM). LVDD is a progressive condition and an independent predictor of mortality in diabetic patients. The etiopathogenesis of LVDD is multifactorial, including diabetes associated comorbidities, such as hypertension, coronary atherosclerosis and obesity, as well as myocardial vascular and metabolic disturbances which lead to diabetic cardiomyopathy. Early stages of LVDD may be detected using echocardiographic techniques. Treatment strategies evolve, based on a better understanding of pathogenic mechanisms, although it is still difficult to efficiently control LVDD evolution. This review synthesizes the main pathophysiological processes and clinical features that characterize DM associated LVDD. Among treatment options, the therapeutic relevance of exercise training programs is underlined.

Key words: *diabetes mellitus, left ventricular diastolic dysfunction, physical training*,

Introduction

Left ventricular diastolic dysfunction (LVDD) is caused by alterations of ventricular diastolic properties with consequences on ventricular stroke volume. It has been shown that nearly half of patients with signs of congestive heart failure have normal ventricular systolic function (1,2), their symptoms being correlated with impaired diastolic function (3,4). It is considered that more than 30% of patients with LVDD and preserved ejection fraction progress to congestive heart failure (5). Community based echocardiographic studies have shown that LVDD has an independent predictive value for all-cause mortality (6).

In diabetic patients, cardiovascular diseases are two to four times more frequent than in the non-diabetic population (7) and are responsible for 80% of diabetic patients' deaths (8). The causes of the association between diabetes mellitus (DM) and cardiovascular diseases are multiple and still incompletely clarified, but coronary atherosclerosis, arterial hypertension (HT) and diabetic cardiomyopathy are important contributors (9).

It has been shown that LVDD with normal ejection fraction is common among people with DM. Its prevalence varies widely (between 47% and 75%) (10,11), possibly because of the different methods used to define and measure LVDD and due to the clinical particularities of the investigated patients. It is largely accepted that LVDD may be the first marker of the preclinical form of diabetic cardiomyopathy. Moreover, it has been shown that LVDD in diabetic patients is predictive of all-cause mortality, independently of HT and coronary artery disease (CAD) (11).

The pathogenesis of LVDD in diabetes is not completely elucidated. Various factors, some of which are directly related to diabetic metabolic disturbances, and others representing comorbidities such as obesity, HT or ischemic heart disease have been extensively investigated.

Diastolic dysfunction is currently evaluated according to the European Society of Cardiology Guidelines, using combined transmitral Doppler flow evaluation and tissue Doppler parameters. The variables recommended for identification of LVDD in patients with preserved LV ejection fraction are: septal e' <7 cm/sec, lateral e' <10 cm/sec, average E/e' ratio >14, left atrial volume index >34 mL/m², and peak tricuspid regurgitation velocity >2.8 m/sec. LVDD is present if more than half of these parameters meet the cutoff values mentioned above (12,13). Recently, other methods have been added, such as the

speckle tracking technique and magnetic resonance imaging, which allow determining early alterations of myocardial mechanics (14).

Treatment of LVDD in DM is complex, covering the suppression of associated risk factors (i.e. obesity, HT, dyslipidemia) and also the pathogenetic mechanisms involved in diabetic cardiomyopathy. Therapeutic methods include both lifestyle interventions and pharmacologic treatment (15). Physical exercise may have favorable effects not only on LVDD risk factors, but also on myocardial structure and function.

The aim of this narrative review is to synthesize the main pathophysiological processes and clinical features which characterize DM associated LVDD. Among treatment strategies, the therapeutic relevance of exercise training programs is emphasized.

Epidemiologic and clinical aspects

The evaluation of LV diastolic function has been investigated in both type 1 and type 2 diabetes mellitus using different non-invasive methods.

The development of diastolic function alterations has been reported in earlier stages of DM and even in prediabetic states, characterized by impaired glucose tolerance or insulin resistance. Celentano *et al.* compared normal glucose tolerance with impaired glucose tolerance and with type 2 DM patients, and found impaired diastolic function not only in subjects with DM, but also in those with impaired glucose tolerance, independently of possible confounding diseases, such as myocardial ischemia, obesity and blood pressure (16). Holzman *et al.* reported a continuous relationship between values of fasting plasma glucose and HbA1C and LVDD in a middle-aged non-diabetic population, suggesting early development of LV alterations even in prediabetic states (17).

In a large study, which investigated the relationship between glucose homeostasis and LV structure and systolic/diastolic function, glucose intolerance and insulin resistance were associated with measures of diastolic dysfunction even in stages preceding the development of DM (18).

In newly diagnosed (within 1 month) normotensive type 2 DM subjects aged between 30-60 years, LVDD was present in 41% of patients. The prevalence of LVDD increased with patients' age, being highest among subjects in the 50-60 years age group (66%). The great majority of the patients had evidence of grade I (delayed relaxation time pattern) LVDD. Another significant finding of this study was the association of glycosylated hemoglobin (HbA1C) with LVDD, suggesting the involvement of persistent hyperglycemia in diastolic function alteration (19). In young asymptomatic DM patients (mean age 29 years) without associated cardiovascular diseases, the prevalence of LVDD was 30% and an alteration of LV function was found even in subjects with less than 6 months diabetes duration. Women were twice more affected than men (10).

In a study that included 456 postmenopausal normotensive DM women who had had the disease for more than 5 years, the authors reported a higher prevalence of LVDD compared to controls. The presence of LVDD was associated with a BMI >30 kg/m^2 and with poor glycemic control, assessed by HbA1C >7.5% (20). Moreover, Leung *et al.* found that weight loss and improved glycemic control had additive beneficial effects on improving both diastolic and systolic LV functions in overweight patients with type 2 DM (21), suggesting a possible involvement of obesity and altered glycemic control in the development of myocardial changes. In order to evaluate whether DM per se, in the absence of arterial HT and CAD, affects LV structure and function, Loncarevic *et al.* compared four groups: group 1 - asymptomatic DM patients without HT and CAD, group 2 - DM patients with HT but without CAD, group 3 - DM patients with CAD and no HT and group 4 – healthy controls, using conventional and speckle tracking echocardiography. Their results indicated that cardiac structure alterations (increased LV mass, LV concentric remodeling, and left atrial enlargement) and impaired LV diastolic and systolic function were associated with the presence of DM independently of age, gender, BMI, HT and CAD. Asymptomatic DM patients without HT and CAD and preserved LV ejection fraction had increased LV mass associated with impaired LV systolic and diastolic function compared to controls (22). Diastolic dysfunction and cardiac hypertrophy, in the absence of CAD and HT, are considered two major characteristics of diabetic cardiomyopathy (23). However, a great number of DM patients, especially elderly diabetics, also have HT, a common cause of LVDD (24). The influence of DM and HT on LVDD was evaluated in a community based cohort, without overt cardiovascular disease. The results indicated that DM and HT had an independent negative effect

on LV diastolic function. When patients had both diabetes and HT, a higher LV end-diastolic pressure was found compared with either condition alone, suggesting an additional risk for the occurrence of LVDD in these patients compared to those with HT alone (25). Nevertheless, in patients without concomitant disease such as HT and CAD, followed up for 6 years, the authors reported that the prevalence of LVDD was relatively low, suggesting that in the early stage of LVDD, there may be a slow progression of myocardial changes (26).

Duration of diabetes, age and abnormally elevated levels of Hb1AC were independently correlated with LVDD in several studies (15,21,27,28,29). An independent relationship between LVDD and BMI was also reported (18,22,28). Other studies found no independent correlation between alteration of diastolic function and poor glycemic control (19,23).

Women seem to be more predisposed than men to develop LVDD (10,15,26). Moreover, in middle-aged and elderly Korean patients at risk of developing CAD, the correlation between metabolic syndrome components and LVDD was more pronounced in women than in men, suggesting a possible role of sex hormones in metabolic syndrome associated LV diastolic function alterations (30). Subclinical myocardial dysfunction was also identified in women with gestational diabetes, using speckle tracking echocardiography (31).

Pathogenesis

The pathogenesis of LVDD in patients with DM is complex and the mechanisms are largely intricated. Myocardial structure and function alteration may be caused by diabetes associated comorbidities or by diabetes specific metabolic or vascular dysfunctionalities.

Various causes may be involved in the development of LVDD in patients with DM, the most important being CAD and systemic HT. According to the Framingham study, CAD is twice more common in diabetic compared to non-diabetic subjects (32). Diabetes accelerates the development of atherosclerosis (5), while atherosclerotic CAD is a well known cause of LVDD. Coronary atheroma formation leads to coronary obstruction, plaque thrombosis and distal emboli with asymptomatic myocardial microinfarctions that may cause myocardial function alterations (33). Arterial HT, associated in more than 50% of patients with DM (34), induces LV hypertrophy and, subsequently LVDD.

Alteration of central arterial distensibility and development of arterial stiffness are common in diabetic patients. Arterial stiffness increases LV afterload and may contribute to LVDD (35). Increased circulating volume, due to sodium and water retention, and increased peripheral vascular resistance caused by insulin resistance and hyperinsulinemia may also induce LVDD (8).

In 1972, diabetic specific cardiomyopathy was described for the first time in four patients with diabetes and heart failure but without HT and coronary atherosclerosis, on histological examination of their hearts (36). Diabetic cardiomyopathy is suspected in clinically asymptomatic patients with LVDD. The pathogenesis of diabetic cardiomyopathy is not completely elucidated, but important metabolic and vascular alterations may be involved. One of them is the decrease of glucose metabolism causing stimulation of free fatty acids beta-oxidation (37,38). Another possible consequence of altered glucose metabolism is the accumulation of advanced glycation end products which affects calcium metabolism, favors apoptosis, with consequences on ventricular function (39). Hyperglycemia may activate the renin-angiotensin system, which stimulates oxidative stress, apoptosis and necrosis, with an increase in interstitial fibrosis (40). Both hyperglycemia and hyperinsulimenia may stimulate myocyte hypertrophy, which is accompanied, during evolution, by LVDD (18,41).

Cardiac microvascular disease in DM reduces coronary flow reserve, in the absence of atherosclerosis of epicardial coronary arteries (42), causing myocardial cell damage and subsequently, myocardial fibrosis (43). Histological examination of cardiac tissue has identified, in autopsy studies, more important interstitial and perivascular fibrosis in diabetics than in hypertensives. Fibrosis was even more pronounced when DM and HT were associated (44). The positive correlation between the duration of diabetes and the presence of LVDD suggests the involvement of microangiopathy and fibrosis in diastolic function alteration (11).

Autonomic dysfunction in DM patients may disturb autoregulation of coronary blood flow. A significant correlation between the severity of cardiac autonomic neuropathy and parameters of LV diastolic function has been reported in echocardiographic studies (45).

Vagal impairment leads to sympathetic overactivity which stimulates the renin-angiotensin-aldosterone system and heart rate, increases stroke volume and peripheral vascular resistance (45,46).

Systemic inflammation, in the presence of cardiovascular risk factors, may affect myocardial structure and function. The results of a prospective 4-year follow-up study showed that C-reactive protein predicted the development of LVDD in patients with type 2 DM (47).

Elevated levels of fasting triglycerides, frequently found in DM, may cause myocardial steatosis, a possible cause of left ventricular function alterations. In a prospective study, triglyceride levels were predictive for the development of LVDD in diabetes (8).

Obesity may be another important contributor to DM associated LVDD, via complex mechanisms including increased insulin resistance, systemic inflammation and oxidative stress, activation of the sympathetic nervous system and increased circulating blood volume (8).

Treatment strategies. Physical training as a therapeutic agent

Even though great progress has been made, treatment of LVDD in DM is still challenging because of the multiple comorbidities and complex mechanisms involved in its pathogenesis.

Treatment strategies

Therapeutic strategies include lifestyle measures and pharmacologic therapies.

Among lifestyle interventions, regular physical exercise and diet play an essential role, due to their immediate and long-term health advantages. Smoking cessation has additional benefits in preventing atherosclerotic vascular complications.

Pharmacologic treatment includes antidiabetic drugs, blood pressure and lipid lowering medication, and metabolic modulators.

Among antidiabetic drugs, metformin, thiazolidinedione, glucagon-like peptide, DPP-4, dipeptidyl peptidase and empagliflozin showed to have favorable effects on LV diastolic structure and/or function (49). Diabetes medication, along with diet, aimed at obtaining good glycemic control, is mandatory for all patients. In a 6-year prospective evaluation of diabetic patients with good glycemic, blood pressure and BMI control, LVDD developed in a small percent of patients and more than 50% of those with mild to moderate LVDD returned to normal diastolic function (50).

Treatment of HT with vasoactive medication, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta-blockers, improves symptoms and reduces mortality in DM patients with heart failure. Angiotensin II receptor blockers and angiotensin converting enzyme inhibitors (ACEI) may protect against ventricular fibrosis and alteration of diastolic function.

Treatment of hypercholesterolemia with statins reduces myocardial fibrosis and inflammation, improving LV function.

Metabolic medication such as trimetazidine and ranolazine showed to have favorable effects on endothelial function and myocyte calcium metabolism.

Novel medication includes antioxidants and cell- and genetic-based therapies.

All these medications have been recently reviewed and are beyond the scope of this article (8,49,51).

Exercise training in DM associated LVDD. Pathophysiological bases and clinical data

Exercise has been shown to improve glycemic control, reduce weight and blood pressure, and ameliorate vascular function and lipid profile (52).

Besides these positive effects on LVDD risk factors, a possible involvement in myocardial metabolism has been investigated. Moreover, extensive research is being carried out to elucidate the molecular mechanisms underlying the effects of exercise on LVDD in diabetic patients.

Both experimental and clinical studies have consistently shown that exercise may slow, or even regress, the development of diabetic cardiomyopathy. Decreased LV function, especially diastolic function, in a rat model of high-fat and high-sugar diet-induced diabetic cardiomyopathy was significantly improved after 8 weeks of aerobic and resistive exercise training (53).

In streptozocin induced diabetic cardiomyopathy, Woodiwiss *et al*. found increased myocardial stiffness caused by enhanced formation of myocardial collagen advanced glycosylation end products. Exercise attenuated the development of abnormal diastolic function without influencing the accumulation of advanced glycosylation end products, suggesting that exercise may influence active properties of the myocardium rather than its structure (54). In another study, exercise training was

initiated 3 weeks after the onset of diabetes and lasted for 4 weeks. The authors reported that exercise training may attenuate the perturbations in intracellular calcium metabolism in the diabetic myocardium (55). Amelioration of LVDD under physical exercise conditions has also been linked to a decrease in inflammatory and oxidative stress mediators, renin-angiotensin-aldosterone system activity and circulating catecholamines (56,57,58).

The advantages of physical training have been confirmed in several human studies. In a 3-year prospective study, 250 type 2 DM patients were randomized to a supervised exercise program, thought to provide at least moderate exertion, using a combination of both aerobic and resistance exercise, or to usual care. The results indicated that in 187 patients who underwent follow-up, an independent positive effect of the exercise program on the development or progression of abnormal diastolic function was found. Nevertheless, the intention-to-treat analysis was negative, which attested the difficulties of maintaining adherence to this form of therapy (59). Young female patients with type 1 DM, who underwent regular submaximal aerobic exercise over 20 weeks, presented clinically significant improvements in aerobic capacity and LV function. Ventricular function amelioration was the consequence of improved filling pressures and increased LV contractility (60). A study that included type 2 DM patients without coronary disease, having different degrees of LVDD, reported an improvement in exercise capacity and normalization of LVDD parameters after aerobic exercise training (3-month aerobic exercise using a cycle ergometer) (61).

Twenty-one men aged 49.8±1.7 years with type 2 DM and no previous history of cardiovascular disease participated in a soccer training group for 1 hour, twice a week. After 24 weeks, LV diastolic function parameters were improved and LV filling pressures decreased. At the same time, the results showed that soccer training increases exercise capacity and lowers blood pressure in men (62).

However, negative results were obtained in one study which included 48 men with type 2 DM (no more than 3 years after confirmation of DM), without known cardiac disease, randomized to supervised high-intensity training four times a week and standard therapy or to standard therapy alone for 12 months. The authors aimed to evaluate whether the reduction of risk factors ameliorates LV diastolic function. Despite a significant reduction of risk factors, particularly blood pressure, and improved diabetic control, exercise training did not influence LV filling pressures and myocardial deformation. The authors speculated that more intense and much longer exercise programs are needed to reduce myocardial alterations (63).

Even though the great majority of experimental and clinical studies indicate a beneficial effect of exercise training on LV diastolic function, large randomized control trials are required to confirm exercise efficacy and to establish the intensity and duration of the exercise programs.

Conclusions

Patients with DM have a significant risk of LVDD, which is associated with worse prognosis and increased mortality. The etiopathogenesis of LV diastolic abnormalities is complex and multifactorial, including diabetes comorbidities, such as HT, CAD, obesity and hyperlipidemia, as well as diabetic cardiomyopathy. Patients' age, diabetes duration, poor diabetes control and female gender may increase the risk of LVDD. Treatment strategies consist of lifestyle health patterns and pharmacologic treatment aimed at maintaining good glycemic control, normal blood pressure and plasma lipids. Physical exercise plays an important role, helping diabetic patients to better control cardiovascular risk factors. Experimental and clinical studies evaluating the effects of exercise on LVDD are encouraging, showing an amelioration of diastolic function parameters. However, large randomized controlled clinical studies are needed to better document and predict the favorable effects of exercise training on LVDD in diabetic patients.

Conflict of interest

The authors declare that there is no conflict of interest.

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