ABSTRACT

Diabetes mellitus is growing at an epidemic proportion across the globe and increasing burden of cardiovascular disease. There is an increasing recognition that diabetes patients suffer from diabetic cardiomyopathy – a non coronary complication of diabetes.

Diabetes cardiomyopathy has a long latent phase which is asymptomatic followed by overt signs of congestive heart failure. The diagnosis of diabetic cardiomyopathy depends on exclusion of coronary artery disease and presence of LV dysfunction on commonly performed investigation like 2D Echocardiography. Treatment of overt congestive heart failure is more or less similar to treatment of congestive heart failure due to any other cause. Novel therapy for treatment of diabetic cardiomyopathy is need of the hour.

INTRODUCTION

The epidemic of diabetes mellitus is of growing concern. Global studies have projected that the number of adults affected with diabetes will increase from 135 million in 1995 to 300 million by 2025. 80% of deaths among diabetic patients is due to cardiovascular disease and much of which has been attributed to Coronary Artery Disease (CAD). However, there is an increasing recognition that diabetic patients suffer from an additional cardiac insult termed ‘diabetic cardiomyopathy’. This entity was originally described by Rubler et al in 1972 on the basis of observations in four diabetic patients who presented with heart failure (HF) without evidence of hypertension (HT), CAD, valvular or congenital heart disease. Since then, diabetic cardiomyopathy has been defined as ventricular dysfunction (systolic and diastolic) that occurs independently of CAD and HT. The increasing detection of this added cardiac insult is supported by data from epidemiological, molecular as well as diagnostic studies.

EPIDEMIOLOGY

The prevalence of a diabetic cardiomyopathy in humans is suggested by many epidemiological and clinical studies over the last three decades. The Framingham study was the first epidemiologic study to document the increased incidence of congestive HF in diabetes males (2.4: 1) and females (5:1) independent of age, HT, obesity, CAD and hyperlipidaemia.

Similar results had been obtained from studies using independent population databases which showed increased HF rates in subjects with diabetes mellitus in cross-sectional analyses and increased risk for developing heart failure in prospective analyses, even after correction for confounding variables. Many studies of diabetic populations have shown echocardiographic changes consistent with systolic dysfunction and left ventricular (LV) hypertrophy and may suggest an increased risk for the subsequent development of heart failure, particularly in the presence of coexisting HT. It is now believed that diastolic dysfunction precedes the development of systolic dysfunction. The evidence of this is documented in Type-I and Type II DM Patients. Echocardiography performed in 87 patients with Type I diabetes mellitus without known coronary artery disease exposed diastolic dysfunction with a reduction in early diastolic filling, an increase in atrial filling, an extension of isovolumetric relaxation, and increased numbers of supraventricular premature beats. Carugo et al studied similar subjects with uncomplicated type 1 diabetes without clinically apparent macrovascular or microvascular complications and concluded early structural and functional cardiac alterations such as increased LV wall thickness and LV mass index, an age-related decline in ejection fraction, and an age-related increase in diastolic diameter. Similar approaches in well-controlled subjects with type 2 diabetes have shown a prevalence of diastolic dysfunction of up to 30%. The use of flow and tissue Doppler Techniques suggests much higher prevalence of diastolic dysfunction (as high as 40% to 60%) in community surveys and in smaller studies of individuals with type 1 and type 2 diabetes without overt coronary artery disease.

PATHOGENESIS

The pathogenesis of diabetic cardiomyopathy is complex. Autonomic dysfunction, metabolic derangements, abnormalities in ion homeostasis, alteration in structural proteins, and interstitial...
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are some of the proposed hypothesis. Sustained hyperglycemia may also increase glycation of interstitial proteins such as collagen, which results in myocardial stiffness and impaired contractility. Several mechanisms which are involved in decreasing myocardial contractility in diabetes mellitus are (1) impaired calcium homeostasis, (2) upregulation of the renin-angiotensin system, (3) increased oxidative stress, (4) altered substrate metabolism, and (5) mitochondrial dysfunction. A detailed discussion about the mechanisms is beyond the scope of this article.

CLINICAL PRESENTATIONS

One unique feature of diabetic cardiomyopathy is the long progression phase which is completely asymptomatic. It is frequently detected with concomitant HT or CAD in most cases. One of the initial signs is mild left ventricular diastolic dysfunction with little effect on ventricular filling. Also, the diabetic patient may show subtle signs of diabetic cardiomyopathy related to decreased left ventricular compliance or left ventricular hypertrophy or a combination of both. In the jugular venous pulse, a prominent “a” wave can also be noted, and the cardiac apical impulse may be overactive or sustained throughout systole. After the development of systolic dysfunction, left ventricular dilation and symptomatic HF, the jugular venous pressure may become elevated; the apical impulse would be displaced downward and to the left. It is not unusual to find systolic mitral murmur in these cases. These changes are accompanied by a variety of electrocardiographic changes that may be associated with diabetic cardiomyopathy in 60% of patients without structural heart disease, although usually not in the early asymptomatic phase. Later in the progression, a prolonged QT interval may also be indicative of fibrosis. Given that diabetic cardiomyopathy’s definition excludes concomitant atherosclerosis or HT, there are no changes in perfusion or in atrial natriuretic peptide levels up until the very late stages of the disease, when the hypertrophy and fibrosis become very pronounced.

DIAGNOSTIC METHODS

The clinical diagnosis of diabetic cardiomyopathy has two important components: the detection of myocardial abnormalities and the exclusion of other contributory causes of cardiomyopathy. A challenge in the clinical diagnosis of diabetic cardiomyopathy has been the lack of any pathognomonic histologic changes or imaging characteristics associated with the diagnosis. The diagnosis of diabetic cardiomyopathy currently rests on noninvasive imaging techniques.

ECHOCARDIOGRAPHY

Echocardiography is the accepted standard for the assessment of alterations in systolic and diastolic function that occur in diabetes. Nevertheless, there is no consensus on the specific criteria to be used to confirm the diagnosis of diabetic cardiomyopathy. However, it is suggested that the combination of two or more Doppler criteria may be sufficient, and the tissue Doppler imaging of mitral annular motion may be particularly helpful to make the diagnosis.

The earliest sign of diastolic dysfunction is impaired ventricular relaxation and is characterized by decreases in the peak early filling velocity of mitral inflow (E). The rate of decrease of velocity following the E velocity (deceleration time) is also prolonged. As diastolic dysfunction progresses and left atrial pressures increase, the pressure gradient between the left atrium and ventricle rises and the E velocity returns toward normal, producing a pseudonormal mitral filling pattern. During later stages of the disease, as symptoms of HF appear, left ventricular chamber compliance decreases further and causes a restrictive filling pattern to emerge. This pattern is manifested by a high E velocity and lower velocity during atrial (A) contraction. A limitation in interpreting transmitral flow patterns is that alterations in flow velocities are dependent on the loading conditions of the heart. Among other criteria, tissue Doppler imaging of mitral annular motion to determine the ratio of mitral annulus velocity during early diastole (e’) to the velocity of mitral annulus motion during atrial systole (a’) can provide a relatively preload-independent assessment of diastolic function. The ratio of E/e’ has been proposed as a sensitive index of left ventricular filling pressures. E/e’ greater than 10 in spontaneously ventilated and greater than 7.5 in mechanically ventilated patients is both sensitive and specific for the presence of increased filling pressures, and changes in left ventricular filling pressures after volume expansion are accurately assessed by repeated E/e’ determinations. Acute changes in loading conditions may have a profound effect on overall ventricular performance in patients with diabetic cardiomyopathy. Even relatively small increases in afterload may provoke increases in left ventricular filling pressures and lead to congestive HF despite preservation of systolic function. Precipitation of myocardial ischemia during the perioperative period may also exacerbate diastolic dysfunction.

Newer noninvasive tools are being used to assess the presence of LVH and systolic/ diastolic dysfunction which help to provide prognostic information in diabetic patients suspected of having cardiomyopathy.

MRI

MRI is an emerging diagnostic technique that can both perform MPI (myocardial perfusion imaging) and assess MFR (myocardial flow reserve). Furthermore MRI is also a very useful tool to assess diastolic function accurately without the drawbacks observed with echocardiographic assessment of diastolic function.

TREATMENT AND THERAPY

Glycemic Control

Poor glycemic control increases the risk of developing heart failure in diabetes. Evidence suggests that good glycemic control is beneficial in the early stages of myocardial dysfunction. Evidence also suggests that diabetic cardiomyopathy does not
develop in patients with strict control type I diabetes, supporting an important role for hyperglycemia in the pathogenesis of diabetic cardiomyopathy. Microvascular complications in diabetes is caused by hyperglycemia, and because microvascular alterations are thought to contribute significantly to the pathogenesis of diabetic cardiomyopathy, good glycemic control is perhaps the most important component in the overall management of diabetic cardiomyopathy.

Strong recommendations regarding the choice of current glucose –lowering therapies in patients with diabetic cardiomyopathy cannot be made because of lack of evidence. In general, the choice of antidiabetic therapy in diabetic cardiomyopathy should be dictated by clinical characteristics, such as the presence or absence renal dysfunction, risk of hypoglycemia, age, volume status, and concomitant drug therapy.

**Neurohormonal Antagonism**

The important role of the renin-angiotensin-aldosterone system in the pathogenesis of complications in diabetic patients is well described. Evidence supports the use of angiotensin-converting enzyme inhibitors in preventing myocardial fibrosis, cardiac hypertrophy, and myocardial mechanical dysfunction associated with diabetic cardiomyopathy. Evidence suggests a beneficial effect of aldosterone antagonism in diastolic heart failure by virtue of their beneficial effects on cardiac hypertrophy and fibrosis.

**Metabolic Modulation**

Recently the aberrant metabolism in HF is well defined by M. Faadil Essop et al. The therapies that may help in restoring metabolic normalcy are ACE and inhibitors, ARBs & Beta blockers. The metabolic modulators such as Trimetazidine and Perhexilene increase the free fatty acid utilization as substrate. The study of trimetazidine in non ischemic cardiomyopathy has shown improvement in LVEF from 30.9% to 34.8% and reduced acid oxidation.

**Novel Therapies**

Therapies directed toward the prevention and progression of diabetic cardiomyopathy is in the early stages of clinical development and has targeted enhanced fibrosis/collagen deposition or alterations in cardiomyocyte metabolism. Prominent among these novel agents are advanced glycation end product inhibitors (aminoguanidine, alanine aminotransferase 946, and pyridoxamine; advanced glycation end product cross-link breakers (e.g., alanine aminotransferase 711)) and copper chelation therapy (e.g., trientine). Modulators of free fatty acid metabolism, such as trimetazidine, have proven useful in the management of angina but their efficacy on diabetic cardiomyopathy is unknown. Most of the above agents are in experimental stages and have not been approved for use in diabetic cardiomyopathy.

**CONCLUSION**

Diabetes mellitus is a major public health problem and cardiovascular disease remains the leading cause of morbidity and mortality which needs intervention at multiple levels for prevention. It is believed that cardiovascular mortality is solely due to atherosclerosis and its complications. Now there are compelling data available from epidemiological and clinical studies suggesting increased risk of cardiac heart failure irrespective of other risk factors. Needless to say coexisting morbidities enhance the likelihood of developing heart failure in diabetes. As mechanisms of cardiomyopathy get unraveled there is a growing possibility of developing novel therapies to treat this not so uncommon noncoronary complications of diabetes – diabetic cardiomyopathy.

**REFERENCES**

15. Sirhem Boudina, PhD; E. Dale Abel, MBBS, DPhil. Diabetic Cardiomyopathy Revisited. (Circulation. 2007; 115:3213-3223.)
16. Zhao XY, Hu SJ, Li J, Mou Y, Chen BP, Xia Q. Decreased cardiac sarco-

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