Clinical manifestations of diabetic cardiomyopathy

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Abstract

Patients with diabetes have an increased incidence of heart failure, even after analyses have controlled for coronary artery disease and hypertension. Thus, as diabetic cardiomyopathy (DCM) has become a well recognized entity among clinicians, a better understanding of its development is necessary for the early diagnosis and the future treatment of diabetes-associated cardiovascular disease. In this article, the latest clinical research on the diagnosis and manifestations of DCM will be outlined. The discussion will be focused on the structural, functional, and metabolic changes that occur in the diabetic myocardium and how these changes contribute to the development of DCM in humans.

Keywords: Diabetic cardiomyopathy, diastolic dysfunction, fibrosis, mitochondrial dysfunction, substrate utilization

Introduction

About three decades ago, Rubler et al [1] first introduced the concept of “diabetic cardiomyopathy” (DCM), which has since been extensively used by epidemiologists and clinicians. DCM is defined as a disease that directly affects the structure and the function of the myocardium, in the absence of other confounding factors such as coronary artery disease (CAD) or hypertension. These early alterations that progress with other diabetes-associated complications lead to the development of more clinically recognized conditions such as left ventricular hypertrophy and heart failure [2].

Structural changes

Left ventricular hypertrophy

Increased left ventricular mass is an independent marker of cardiovascular risk that often occurs independently of arterial blood pressure in type 2 diabetes. Thus diabetes is an independent contributor to left ventricular hypertrophy (LVH) and myocardial stiffness* [3]. The Framingham study investigators used echocardiography and reported a significant increase in left ventricular wall thickness in women with diabetes [4]. This was further confirmed in a follow-up study on the Framingham offspring, which also showed that women with diabetes experienced a steeper increase in left ventricular mass with advancing age compared with men and those without diabetes [5]. In contrast, the Strong Heart Study, conducted in a population of American Indians, found that both men and women with diabetes had greater left ventricular mass and wall thickness [6]. Furthermore, in a multi-ethnic population, the likelihood of having left ventricular mass above the 75th percentile of the distribution was 1.5-fold greater in patients with type 2 diabetes, independently of various covariates, including hypertension [7]. In this same population, it was shown that increased left ventricular mass can be
seen only in patients with diabetes, as compared with patients with impaired or normal fasting glucose concentrations [8], suggesting that alterations in the geometry of the heart in diabetic individuals are not an early defect but, rather, a consequence of changes associated with diabetes such as hyperglycemia or obesity. Indeed, Eguchi et al [7] found a significant interaction between diabetes and central obesity and the risk for LVH. Although associations between type 2 diabetes and LVH have been well studied, the influence of type 1 diabetes on left ventricular mass is not well characterized. For example, increased left ventricular wall stiffness was detected in women with type 1 diabetes [9], but 50% of these patients had microvascular complications and some exhibited abnormalities in autonomic function tests; furthermore, in a small cohort of patients with long-standing type 1 diabetes, improved glycemic control significantly reduced septal thickness and left ventricular mass when compared with those in patients who did not achieve improvement of glycemic control [10]. However, in this study, diabetic patients had other complications that may have affected left ventricular mass independently of diabetes. Indeed, it is known that retinopathy and nephropathy, associated with type 1 diabetes, can also affect myocardial remodeling [11]. In this regard, studies conducted in individuals with uncomplicated type 1 diabetes did not detect LVH [12,13].

**Interstitial fibrosis**

Diabetic cardiomyopathy is characterized by interstitial fibrosis, mainly composed of collagen, and perivascular fibrosis. Regan et al [14] found a significant increase in deposition of collagen around the vessel and between the myofibers in heart biopsies from diabetic patients. In addition, a significant increase in collagen type III, but not type I or VI, was found in endomyocardial biopsies obtained from patients with type 2 diabetes, free of CAD and hypertension [15]. Furthermore, diastolic dysfunction detected in a population of patients with uncomplicated type 2 diabetes correlated with pro-collagen type I carboxy-terminal peptide [16], suggesting a mechanistic involvement of myocardial fibrosis in the myocardial dysfunction that occurs in diabetes.

**Increased cell death and oxidative stress**

Diabetes is associated with myocyte cell death; however, it is unclear whether diabetes can directly activate cell death or, rather, it activates pathways known to induce this process. Indeed, activation of the renin–angiotensin system (RAS) was associated with increased oxidative stress and cardiomyocyte and endothelial cell death in hearts of patients with diabetes [17,18]. Thus inhibition of the RAS reduced the rate of first admission to hospital from heart failure and improved echocardiographic indices of left ventricular diastolic function in patients with type 2 diabetes [19,20]. The mechanisms by which cell death occurs in the human myocardium are still not well understood. Thus, where both forms of cell death (necrosis and apoptosis) were identified in myocardium biopsies of patients with diabetes, apoptosis was maximally induced in the diabetic myocardium, whereas necrosis was exaggerated by hypertension[17]. Recently, Chowdhry et al [21] showed that apoptosis and necrosis were increased in the right atrial appendage of patients with type 1 and type 2 diabetes, and that inhibition of caspase-3 reduced apoptosis without influencing necrosis, whereas inhibition of poly-adenosine diphosphate-ribose polymerase reduced necrosis and apoptosis. Although the findings of previous studies have implied that oxidative stress may have a critical role in the development of DCM, this issue has not been properly and fully addressed in humans. The majority of reactive oxygen species (ROS) are generated in the mitochondria. However, enzymatic systems capable of generating ROS in the cytosol – such as NADPH oxidase – can be modulated by hyperglycemia [22]. ROS can also interact with nitric oxide to form nitrotyrosine, which was found to be increased in myocardial biopsies of humans with type 2 diabetes [17]. Finally, studies of the role of antioxidants in preventing cardiac dysfunction in humans have been disappointing. Indeed, in a randomized controlled trial in patients receiving vitamin E, the risk of heart failure was greater in patients receiving the antioxidant treatment [23].

**Myocardial lipotoxicity**

Diabetic myocardium is also characterized by increased deposition of intramyocardial lipids, which can contribute to cell death and thus to cardiac dysfunction. Regan et al [14] identified deposits of lipofuscin, which are brown pigment granules composed of lipid-containing residues, in left ventricular transmural biopsies obtained from diabetic patients. Furthermore, they measured myocardial triglyceride and cholesterol content in these biopsies and found a significant increase. Similarly, Oil Red O staining of heart sections of non ischemic failing hearts revealed an increased deposition of lipid that was exacerbated by diabetes [24]. More importantly, increased myocardial triglyceride in patients with type 2 diabetes was associated with diastolic, but not systolic, dysfunction [25].

**Functional changes**

In the course of DCM, several functional changes develop and progress (Figure 1). It is therefore incumbent upon clinicians to identify these abnormalities,
because early detection and appropriate treatment can prevent worsening of this condition to overt heart failure.

**Diastolic dysfunction**

Diabetic cardiomyopathy in humans is characterized by diastolic dysfunction, which may precede the development of systolic dysfunction. Indeed, echocardiography performed in 87 patients with type 1 diabetes mellitus without known CAD revealed diastolic dysfunction as indicated by reduced early diastolic filling, increased atrial filling, extended isovolumetric relaxation, and increased supraventricular premature beats [26]. Similarly, in individuals with uncomplicated type 1 diabetes without clinically apparent macrovascular or microvascular complications, Carugo et al [27] reported an age-related increase in diastolic diameter. Similar approaches in patients with well controlled type 2 diabetes revealed a prevalence of diastolic dysfunction in up to 30% [28,29]. The use of flow and tissue Doppler techniques suggests an even greater prevalence of diastolic dysfunction in as many as 40% of patients with diabetes [30,31]. In contrast, a study performed in young patients with type 1 diabetes showed that myocardial contractility was not depressed, but rather exaggerated [9]. Similarly, in a recent study patients with type 1 diabetes, myocardial dysfunction was absent despite changes in the structure of the heart [38]. It is important to note that the patients in this study were treated four to five times daily with insulin, which may have prevented contractile dysfunction.

**Systolic dysfunction**

In the context of DCM, systolic dysfunction occurs late, often when patients have already developed significant diastolic dysfunction. Thus, in a population of patients with type 1 diabetes with several degree of complications, systolic dysfunction was observed in 39% of those with complications and in only 6% of those free from complications [34]. In addition, a subtle systolic dysfunction, which is usually characterized by a low left ventricular ejection fraction (LVEF), is often missed when standard 2-dimensional echocardiography techniques are used. Thus studies have emerged that demonstrate subtle abnormalities in systolic function in association with a diagnosis of diastolic dysfunction [35,36]. In a well defined study population of relatively young persons with long-term type 1 diabetes, reduced left ventricular compliance, increased afterload, and decreased myocardial contractility were observed [37]. In contrast, a study performed in young patients with type 1 diabetes showed that myocardial contractility was not depressed, but rather exaggerated [9]. Similarly, in a recent study of patients with type 1 diabetes, myocardial dysfunction was absent despite changes in the structure of the heart [38]. It is important to note that the patients in this study were treated four to five times daily with insulin, which may have prevented contractile dysfunction.

**Impaired contractile reserve**

Diabetic cardiomyopathy involves several stages of disease, including a period in which symptoms are not present, and resting left ventricular dimension and function are still normal. In this early phase, left ventricular dysfunction can be characterized by exercise. Indeed, impaired augmentation of LVEF occurs in as many as 40% of patients with diabetes [39]. Recent reports in both type 1 and type 2 diabetes showed that longitudinal functional reserve (indicated by reduced mitral annular systolic and early diastolic velocities) and left ventricular contractility reserve (indicated by depressed peak exercise left ventricular stroke index, cardiac index, and LVEF) were reduced after exercise [13,40], whereas no change in these parameters was observed at rest. Thus cardiac performance after exercise could be a tool with which to detect early contractile dysfunction in diabetes.

**Metabolic changes**

Studies of altered cardiac metabolism in animal models of diabetes have emerged in recent years, becoming an attractive mechanism contributing to the development of DCM. In this section, we will discuss the recent findings supporting the existence of altered cardiac substrate metabolism and mitochondrial dysfunction in the heart of humans with diabetes.

**Altered substrate utilization**

The main characteristic of diabetes is an increase in serum glucose and free fatty acid (FFA) concentrations. Thus the diabetic heart relies almost
Mitochondrial dysfunction

In contrast to skeletal muscle, studies examining mitochondrial function in cardiac muscle of diabetic patients have been challenging. Our contribution to the understanding of mitochondrial bioenergetics comes mainly from animal studies of obesity and diabetes [47]. Reagan et al [14] first reported increased numbers of mitochondria with pleomorphism, but no swelling or evident distortion of cristae in the myocardium of patients with diabetes. Using phosphorus-31 nuclear resonance spectroscopy, Clarke’s group provided evidence for decreased cardiac energetics in patients with type 2 diabetic who were free from CAD [48]. Although no direct measure of mitochondrial capacity was provided in this study, mitochondrial generation of ATP was reduced with diabetes, as indicated by the reduction in phosphocreatine/ATP ratios. Finally, studies related to the response of the diabetic heart to ischemic preconditioning have suggested that a defect in the mitochondrial ATP-sensitive potassium channel could explain the inability of the diabetic myocardium to respond to ischemic preconditioning and increase the risk for myocardial infarction [49].

Conclusion

The belief is widely held that the increase in cardiovascular mortality is a consequence of accelerated atherosclerosis. However, compelling epidemiological and clinical data indicate that diabetes mellitus increases the risk for cardiac dysfunction and heart failure independently of other risk factors such as CAD and hypertension. Thus DCM has become a well characterized clinical disease that is manifested by structural, functional, and metabolic changes. It is hoped that, as the mechanisms responsible for DCM continue to be elucidated, they will provide the impetus for generating novel therapies tailored to reduce the risk of heart failure in individuals with diabetes mellitus.

*See glossary for definition of this term.*

REFERENCES

Main clinical article

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