

Diabetes Mellitus and Cardiac Function: beyond Ischemic Heart Disease

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From a clinical perspective, quite often in day-to-day clinical practice many patients with Diabetes Mellitus come along in the emergency room with symptoms of heart failure or/and pulmonary edema. Many times the usual diagnosis after exclusion of ischemic heart disease, is Left Ventricular Diastolic Dysfunction (LVDD) with preserved left ventricular systolic function. Two distinguished mechanisms seem to be implicated after the exclusion of hypertension, also. Those are diabetic cardiomyopathy and diabetic cardiovascular autonomic neuropathy. In this context, the clinical course of cardiac diastolic dysfunction in diabetes mellitus progresses from subclinical cardiac abnormalities, to severe diastolic heart failure with normal ejection fraction and eventually to systolic dysfunction and at the end by heart failure with reduced ejection fraction. In current review we summarize data about the two aetiopathogenetic mechanisms which lead to LVDD as first manifestation and later to heart failure with reduced left ventricular ejection fraction. Moreover, we summarize clinical evidence that provide substantial indications to improve therapeutic management in early stages of LVDD and could be associated with improved clinical outcome in long-term duration of DM.

Heart failure and its management is the main and seriously growing up medical problem and health problem for the entire population. Disorders of hyperglycemia, hypertension, obesity and dyslipidemia occur more often in either alone or in various combinations in patients with Diabetes Mellitus and they increase substantially the risk of developing diastolic or/and systolic Left Ventricular Dysfunction. The final result is the occurrence of the Heart Failure (HF). Furthermore, many of the antidiabetic drugs used to control hyperglycemia are relatively ‘contraindicated’ in HF as has been reported from large international multicenter studies. Some of them could cause or/and precipitate cardiac dysfunction, although others have a beneficial effect.

Early assessment, diagnosis and management of cardiac dysfunction during the course of diabetes probably will add to the most reduction of cardiovascular events due to ventricular dysfunction and heart failure. Moreover, it is important to address the underlying cause of heart failure, because the specific etiology determines the choice of treatment.

Diabetic cardiomyopathy is initially characterized by myocardial fibrosis, dysfunctional remodeling, and associated diastolic dysfunction, later by systolic dysfunction, and eventually by clinical heart failure. Impaired cardiac insulin metabolic signaling, mitochondrial dysfunction, increases in oxidative stress, reduced nitric oxide bioavailability, elevations in advanced glycation end products and collagen-based cardiomyocyte and extracellular matrix stiffness, impaired mitochondrial and cardiomyocyte calcium handling, inflammation, renin-angiotensin-aldosterone system activation, cardiac autonomic neuropathy, endoplasmic reticulum stress, microvascular dysfunction, and a myriad of cardiac metabolic abnormalities have all been implicated in the development and progression of diabetic cardiomyopathy. Molecular mechanisms linked to the underlying pathophysiological changes include abnormalities in AMP-activated protein kinase, peroxisome proliferator-activated receptors, O-linked N-acetylglucosamine, protein kinase C, microRNA, and exosome pathways.

Diabetic Cardiac Autonomic Neuropathy (DCAN) is a secondary complication related to poor glycemic control and includes abnormalities in

heart rate control, vascular hemodynamics, and cardiac structure and function. An early characteristic of Cardiac Autonomic Neuropathy is reduction of parasympathetic activity with an imbalance toward relatively higher Sympathetic Nervous System (SNS) activity. In this regard, activation of the SNS enhances β -1 adrenergic receptor (β 1) signaling that promotes cardiac hypertrophy, interstitial fibrosis, cardiomyocyte apoptosis, and impaired function.

The treatment of LVDD should relieve symptoms and increase longevity. Unfortunately, to date, studies of neurohormonal blockade in patients with LVDD have failed to show a mortality benefit or a clear improvement in quality of life. Inhibitors of the RAAS and sympathetic nervous system should continue to be used in the population of patients with LVDD who have diabetes mellitus despite the fact that the use of these drugs for the primary treatment of LVDD remains unsupported by the available evidence from large studies. But in small studies with well characterized patients ACE-Inhibitors have been shown to improve both LVDD and Cardiac Autonomic Dysfunction simultaneously after one year of treatment.