Management of diabetic cardiomyopathy: the implications for low resource settings

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Abstract

Cardiovascular diseases are the commonest cause of mortality in people living with diabetes mellitus. Prominent among the various cardiovascular diseases complicating diabetes is diabetic cardiomyopathy. It is characterized by cardiac dysfunction in a patient with diabetes having excluded other causes of cardiac dysfunction such as coronary heart disease, hypertensive heart disease and valvular heat disease.

Diabetic cardiomyopathy has chronic hyperglycemia as the central theme of its pathophysiology. In the early phase, it is asymptomatic. In the late phase, it presents with heart failure. The diagnostic investigation of choice is echocardiography. Treatment is aimed at optimizing glucose control and using cardioprotective medications such as GLP-1 agonists and SGLT-2 inhibitors.

Managing the disease has myriads of implications for low resource settings. Prevalence of diabetes is increasing at higher rate in these nations and it is expected that the incidence of diabetic cardiomyopathy will rise faster in these regions. More researches need to be focused in this direction as the data from low resource settings about diabetic cardiomyopathy is very scanty. The availability of the diagnostic tools in low resource settings is inadequate and this may delay diagnosis. Also, drugs like sulphonylureas and thiazolidinediones which are cheap and readily available but which may increase the chance of heart failure are still commonly used in low resource settings. Cardioprotective medications such as GLP-1 agonists are unaffordable and not readily available in low resource settings.

This review aims to highlight the implications of managing diabetic cardiomyopathy in low resource settings so as to divert more attention to the disease, in terms of research and policies. These will help to alleviate the burden of diabetic cardiomyopathy in low resource settings.

Background

Diabetic cardiomyopathy is one of the cardiovascular complications of diabetes mellitus and it is characterized by cardiac dysfunction which can lead to heart failure.[1] It is often diagnosed late because it is usually asymptomatic until it presents in frank heart failure. This is a challenge in low resource settings where the management of heart failure is still lagging behind when compared with the developed world. In patients with diabetes, presence of co-morbidities such as hypertension, obesity and coronary artery disease make the aetiology of heart failure difficult to determine during the initial evaluation of the patient. The capacity to do investigations to screen for possible differential diagnoses when a diabetic patient presents with heart failure is limited in low resource settings. Therefore, the diagnosis of diabetic cardiomyopathy is often difficult to make when a diabetic patient presents with heart failure in low resource settings.

Cardiovascular disease is now a prominent cause of mortality in low resource settings due to epidemiologic and demographic transition.[2] Diabetes mellitus is a prominent risk factor for cardiovascular disease. Therefore, since the prevalence of diabetes is rising in the underdeveloped world due to westernization, obesity and urbanization, it is expected that cardiovascular disease will soon be in the topmost cause of mortality in the poor resource settings too. There is lack of health care delivery capacity in poor resource settings, where the most common source of health care financing is still out of the pocket. From the findings of the landmark Framingham Heart Study, diabetes mellitus increases the risk of heart failure by 2 among men and by 4 among women, thereby removing the extensively documented cardiovascular risk protection among females.[1] This has a major implication for low resource settings because women are often not financially empowered and cost of care is usually paid out of pocket.

Authors, as far back as the late 19th century, have documented a close relationship between heart failure and diabetes but it was in the later part of the twentieth century before the entity called diabetic cardiomyopathy was identified and described as a distinct pathology.[3] The documented criteria to diagnose diabetic cardiomyopathy include abnormal left ventricular hypertrophy associated with diastolic dysfunction and/or reduced ejection fraction.[3]Diabetic cardiomyopathy is a diagnosis of exclusion and it is defined as ventricular dysfunction in patients with diabetes having excluded hypertensive heart disease, valvular heart disease and coronary heart disease.[4] Based on this definition, it is estimated that 10-18% of patients with diabetes have diabetic cardiomyopathy.[5]

Diabetes mellitus causes structural and functional changes in the myocardium. The underlying theme in these changes is chronic hyperglycaemia. Some of the mechanisms of myocardial damage that have been reported include lipotoxicity, glucotoxicity, oxidative stress, calcium imbalance, chronic inflammation with fibrosis and apoptosis.[6] Animal studies have helped to shine more light on the pathophysiologic mechanisms of diabetic cardiomyopathy.[7] In diabetic animals, (with diabetes induced with streptozocin or alloxan or fed with high fat diet or through genetic mutation of the leptin system), cardiac abnormalities similar to what is found in diabetic cardiomyopathy in diabetic humans were demonstrated.[8]

Epidemiology

Data on the epidemiology of diabetic cardiomyopathy is scanty. In a population-based study done in Olmsted County, the reported prevalence of diabetic cardiomyopathy was 16.9%.[10] 54.4% of the patients with diabetes had some degree of diastolic dysfunction but did not meet the criteria for diabetic cardiomyopathy. The risk of developing heart failure from diabetic cardiomyopathy was 22%. The cumulative probability of death at 9 years among those who had diabetic cardiomyopathy was 18%. According to the Olmsted County study[9] a diabetic heart has the risk of left ventricular dysfunction, diastolic dysfunction and systolic dysfunction increased by 1.9, 1.7 and 2.2 times respectively. Moreover, in a study on the cardiovascular complications of diabetes mellitus in sub-Saharan Africa by Kenge *et al* showed that echocardiographically defined cardiac abnormalities were present in about 50% of the diabetic population but stringent criteria were not applied to identify diabetic cardiomyopathy.[10]

A report has quoted the 1 year mortality from advanced diabetic cardiomyopathy to be as high as 20%.[11] Patients with diabetic cardiomyopathy who have heart failure with preserved ejection fraction are twice more likely to be admitted into the hospital for heart failure compared with patients without diabetes but who have heart failure with preserved ejection fraction.[12] The risk factors for the development of heart failure from diabetic cardiomyopathy include advanced age, suboptimal glycemic control, obesity and the presence of microvascular complications such as diabetic neuropathy or nephropathy.[13] The use of certain glucose lowering agents such as thiazolidinediones and sulphonylureas are associated with increased risk of heart failure in patients with diabetes, This is significant for patients in low resource settings because drugs such as sulphonylureas are cheap, readily available and commonly used in such settings. However, paucity of data in low resource settings gives the impression that the disease is rare and this has prevented adequate attention from being paid to diabetic cardiomyopathy by the policy makers, therefore current research funding is not geared towards its direction.

Pathophysiology

Despite decades of intense research, the pathophysiology of diabetic cardiomyopathy is not well defined but there are theories proposed by different authors to explain the mechanisms of the disease. There are multiple mechanisms that interplay at the molecular or cellular level but the main culprit is chronic hyperglycaemia. The generation of reactive oxygen species or nitrogen species from metabolic abnormalities such as hyperglycaemia and chronic inflammation are the final pathways in the development of diabetic cardiomyopathy.[14] These metabolic injuries induce some adaptive responses in the heart and when the adaptive responses cannot cope, heart failure ensues.

Oxidative stress from chronic hyperglycaemia induces deoxyribonucleic acid (DNA) damage. In an attempt to repair the damage, glucose is shunted from the usual glycolytic pathways to other metabolic pathways such as hexosamine or polyol pathway. Eventually, molecules such as advanced glycation end-products (AGEs) are produced.[15] These AGEs crosslink collagen and elastin fibres leading to increased myocardial stiffness and reduced cardiac relaxation.

Damaged DNA can also induce apoptosis of cardiac myocytes which are replaced with fibrous tissue causing a stiffened myocardium with resultant diastolic dysfunction.

The commonest type of diabetes, type 2 diabetes, is associated with insulin resistance and hyperinsulinaemia. Hyperinsulinaemia causes genetic and epigenetic changes that lead to the activation of transcription factors and eventually, increased synthesis of cellular and extracellular proteins.[16] The continuous deposition of these cellular and extracellular proteins lead to cardiac hypertrophy and fibrosis.

Microvascular ischaemia has also been documented in the pathophysiology of diabetic cardiomyopathy. Hyperglycaemia is associated with endothelial dysfunction and hyaline deposition in the medial layer of arterioles.[14]These pathogenic changes cause myocardial ischaemia which leads to myocardial stiffness and diastolic dysfunction.

Clinical presentation

Early onset diabetic cardiomyopathy is largely asymptomatic. This is called the subclinical phase of the disease. At this stage, detection of diabetic cardiomyopathy is through echocardiography. It is characterized by mild left ventricular hypertrophy and diastolic dysfunction. The isovolumetric relaxation time is increased, on echocardiography. Unfortunately, in most low resource settings, echocardiography may not be performed at this early stage and the disease may never be diagnosed until the patient presents in heart failure, at which stage, the prognosis is not very good.

Later on, the patient develops symptoms of congestive cardiac failure. This is the clinically evident or symptomatic phase. Symptoms such as breathlessness, fatigue, cough and pedal swelling become prominent. On physical examination, the jugular venous pressure may be increased, the apical impulse is displaced leftwards and downwards. The character may be heaving. An additional heart sound (third or fourth heart sound) may be heard. There may be a systolic murmur on auscultation.

Diagnosis

In order to make diagnosis of diabetic cardiomyopathy, there is a need to take a detailed history and perform a thorough physical examination. Thereafter, relevant investigations are requested to substantiate the clinical suspicion or exclude close differential diagnoses. Chest radiographs may show upper lobe diversion, interstitial or alveolar infiltrate, enlarged cardiac silhouette, features of effusion, peribronchial cuffing and batwing appearance. Electrocardiography may show features of left ventricular hypertrophy, various forms of arrhythmias, prolongation of the QTc. Biomarkers of heart failure such as brain natriuretic peptide or myocardial necrosis such as troponins may be useful. In low resource settings, many of these investigations are expensive and not readily available. This negatively affects the quality of care given to such patients.

Echocardiography is a non-invasive approach to diagnose diabetic cardiomyopathy. It is the gold standard of diagnosis.[1] it is useful in identifying structural disorders of the heart. It can

detect features of left ventricular hypertrophy and impaired diastolic function which are seen in the early phase of diabetic cardiomyopathy. Besides being a diagnostic tool, echocardiography can also be used to assess response to treatment and progression of the disease. Two dimensional echocardiography can assess the structures of the heart and their movement. Majority of the health facilities in low resource settings do not have facilities for echocardiography and it may be difficult to diagnose the disease.

In addition, other radiological investigations that play a role in the diagnosis of diabetic cardiomyopathy include cardiac magnetic resonance imaging which can assess moving fluids in specific areas such as the valves; nuclear imaging such as positron emission tomography (PET) and gated single-photon emission computed tomography (G-SPECT) also play a crucial role towards the diagnosis of diabetic cardiomyopathy. However, all these investigations are not readily available in the low resource settings.

Furthermore, the ideal test to confirm diabetic cardiomyopathy is endomyocardial biopsy. This is invasive and it may require special staining to be able to appreciate pathologic changes that are found in dilated cardiomyopathy. The expertise for this kind of invasive produce is readily available in low resource settings and are often not done.[1]

Treatment

The interest in diabetic cardiomyopathy has been growing in the past few decades. In spite of this, there are no universal guidelines specific for the treatment of diabetic cardiomyopathy. Optimal glycemic control through the use of pharmacologic and non-pharmacologic approaches is central to the treatment of diabetic cardiomyopathy. Studies [ref] have reported that majority of individuals with type 2 diabetes in some sub-Saharan African countries do not have optimal glycemic control. In this scenario, giving an acceptable standard of care for diabetic cardiomyopathy in the absence of good glycemic control may be difficult.

Interestingly, the newer glucose lowering agents such as glucagon-like peptide 1 agonists (GLP-1 agonists) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors have not only glucose -lowering ability but also some other beneficial effects on the cardiovascular system independent of their glucose lowering effect. In fact, the Federal Drug Agency and European Medicine Agency require cardiovascular outcome trial for newer glucose lowering agents before they are granted approval to be used by the diabetic populace [ref]. These drugs are however expensive and are not affordable to the majority of the individuals living with diabetes in low resource settings.

In patients that have progressed to heart failure, the heart failure regimens that have been proven to improve survival can be used in them. These include angiotensin-converting enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists and cardio-selective beta-blockers.

Conclusion

The prevalence of diabetes mellitus is rising globally but at higher rate in the developing world. As the diabetes prevalence is rising, the complications are also rising. A major but often overlooked complication of diabetes is diabetic cardiomyopathy. It is characterized by

left ventricular hypertrophy and impaired diastolic function. The pathophysiologic mechanisms of diabetic cardiomyopathy are multifactorial. The gold standard diagnostic procedure is echocardiography. Optimal glycaemic control, especially with the use of GLP-1 agonists and SGLT-2 inhibitors, are central to the treatment of diabetic cardiomyopathy.

The implications of this disease to low resource settings are multifactorial. Firstly, there is paucity of data from low resource settings about the disease and much attention is not paid to it. The early phase of diabetic cardiomyopathy often go undiagnosed in low resource settings as routine echocardiography is the exception and not the rule. The capacity to employ diagnostic tools such as echocardiography is limited and this makes it difficult to be able to diagnose diabetic cardiomyopathy as it is a diagnosis of exclusion. The use of the newer drugs which have cardioprotective benefits apart from glucose lowering effects are not readily available and not affordable in low resource settings. In essence, the prognosis of diabetic cardiomyopathy may be worse in the low resource settings. These challenges are highlighted so that studies can be designed on how to overcome the various issue raised in this article

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