Diabetic Cardiomyopathy: Five Major Questions with Simple Answers

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Abstract

Diabetes is a major risk factor for heart disease. Diabetic cardiomyopathy is a long-lasting process that affects the myocardium in patients who have no other cardiac conditions. The condition has a complex physiopathology which can be subdivided into processes that cause diastolic and/or systolic dysfunction. It is believed to be more common than reported, but this has not been confirmed by a large study. Diagnosis can involve imaging; biomarkers cannot be used to identify diabetic cardiomyopathy at an early stage. In people with diabetes, there should be a focus on prevention and, if diabetic cardiomyopathy develops, the objective is to delay disease progression. Further studies into identifying and managing diabetic cardiomyopathy are essential to reduce the risk of heart failure in people with diabetes.

Keywords

Diabetic cardiomyopathy, diabetes, metabolic disease, heart failure, myocardial dysfunction

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Type 2 diabetes is a major risk factor for the development of heart disease.[1] At the beginning of the last century, or even before, several authors described a possible association between diabetes and heart failure (HF).[2] However, according to the Heart Failure Association of the European Society of Cardiology guideline for the treatment of type 2 diabetes and HF, the first report of this association, excluding other risk factors, was published in 1954.[3]

Lundbaek et al. stated that a heart condition could occur without hypertension or coronary artery disease.[3] Later, in 1972, Rubler et al. reported a series of pathological changes in myocardial tissue in four patients with diabetic glomerulosclerosis.[4] They described diffuse fibrotic strands extending between bundles of muscles and and myofibrillar hypertrophy. Soon after, researchers working on the Framingham Heart Study demonstrated a higher incidence of HF in women and men with diabetes, with an increased prevalence of cardiovascular complications.[5]

A search of Medline for 'diabetic cardiomyopathy' in November 2018 retrieved 1,002 articles published in the past 5 years (almost 50% of total published articles), which indicates that interest in diabetic cardiomyopathy (DCM) is growing. However, the condition continues to be unrecognized. Several technological advances are needed to make an accurate diagnosis, and this technology that may not be available in middle- and low-income countries, where the prevalence of diabetes is increasing, while effective treatment is lacking, predisposing these patients to DCM.

What is Diabetic Cardiomyopathy?

Rubler et al. are believed to be the first to describe DCM.[4] However, those findings are not useful from a clinical point of view because pathological findings are not a suitable way to diagnose this condition. Descriptions of the condition, with varying degrees of complexity, have been published.[1,6,7] They all have something in common: a disease of a heart muscle develops in patients with diabetes who have no other cardiac conditions such as valvular, ischemic, or hypertensive disease. A novel definition has been proposed: DCM is a long-term process that affects the myocardium from the early stage of metabolic changes.[8]

Nevertheless, others have reported that it is purely a combination of molecular myocardial abnormalities that predispose a person to develop myocardial dysfunction, starting with type 1 or type 2 diabetes, which is a metabolic disease. These metabolic changes elicit cardiac functional abnormalities and, ultimately, cardiac dysfunction.[9]

Is Diabetic Cardiomyopathy Common or Rare?

Unfortunately, the definition of DCM can cause problems in answering this question. Patients with a history of hypertensive or ischemic disease cannot be diagnosed with DCM. Observational registries show that epicardial coronary stenosis of clinical importance occurs in 90% of patients with diabetes, and others report more than three-quarters of patients with diabetes have hypertension.[10,11] As a result, the prevalence of DCM in the whole diabetic population is less than 8%, but this figure is likely to be wrong. Diastolic dysfunction can be present in up to 25% of

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patients with diabetes, as several clinical trials have shown, rising to 60% in patients with type 1 diabetes.[12,13] According to recent data, around 600 million people are living with type 2 diabetes.[12] The prevalence of DCM is not clear because of a lack of large study outcomes from different populations with type 2 diabetes.[13]

Does Diabetic Cardiomyopathy Have a Simple Physiopathology?

Unfortunately, the answer is no. DCM is a complex condition that can affect the heart in several ways.[14] Type 2 diabetes involves impaired glucose levels with an increase in insulin resistance. This systemic condition produces changes in the metabolism of cardiomyocytes, which increase their metabolism of fatty acids.[15] This leads to fibrosis and a loss of contractile properties, which decrease the compliance of the heart so cause diastolic dysfunction.

The hexosamine biosynthetic pathway, protein kinase C pathway, advanced glycation end-products pathway, and polyol flux pathway secondary to an increase of hyperglycemia can all produce contractile dysfunction, which can lead to systolic HF in a patient with DCM.[16,17]

Can Diagnosis be Improved?

Yes. Although diagnosis in the early stage is not easy, metabolic changes can be identified using nuclear imaging and MRI.[12] Echocardiography is also useful in the first stage. Several degrees of diastolic dysfunction may appear with the use of longitudinal and circumferential strains.[18]

In the later stages, complementary imaging can produce more information. In the middle stage, echocardiography can be used to determine the mass and diameter of the left ventricle and the diastolic patterns described above. MRI can detect changes in blood flow and ventricular filling patterns.[19]

In the final stages, several degrees of systolic dysfunction become apparent. Perfusion changes can be seen in nuclear imaging. Cardiac tomography can detect calcification and systolic dysfunction; the latter can also be detected by MRI. Echocardiography can show several degrees of contractile dysfunction through alterations of strain rate and global, regional, and ventricular strain.[12,18,19]

Several biomarkers can give additional information, including matrix metalloproteinases (MMPs), tissue inhibitors of MMPs, microribonuleic acid, procollagen 3 N-terminal peptide, and brain natriuretic peptide.[13] Although tests for these have been approved by Food and Drug Administration for the screening of heart diseases, none can be used to identify DCM at an early stage.[20]

Can Treatment be Improved?

Yes. Given that the Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial stated that screening to detect subclinical DCM had failed, further studies into the development of novel strategies are essential to reduce the risk of HF in people with diabetes.[1,21]

Hypoglycemic agents are the cornerstone of type 2 diabetes treatment. However, none of them had been shown to decrease the risk of HF until the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and CANagliflozin cardioVascular Assessment Study (CANVAS) trialS, which examined empagliflozin and canagliflozin respectively.[6,22]

Other strategies proposed for DCM treatment include lifestyle modifications, vasoactive medications (such as beta-blockers and angiotensin-converting enzyme inhibitors), lipid-lowering drugs (such as statins), and metabolic modulators.[8,23,24]

A classification for DCM has been created, using similar categories to the New York Heart Association (NYHA) system. Patients with grade 3 DCM can be categorized as having NYHA grade 2 or 3 and DCM grade 4 can have a NYHA classification of 3 or 4. The difference between these two classifications is that while NYHA is a clinical classification for HF, DCM grades depend on the metabolic status: impaired glucose tolerance (grade 1), chronic hyperglycemia (grade 2), insulin resistance or microangiopathic complications (grade 3), and macroangiopathic complications (grade 4). Treatment depends on the grade or type of HF and DCM.[25,26]

Conclusion

DCM is a long-lasting process that affects the myocardium in absence of valvular, hypertensive, or ischemic heart diseases. It seems that it is more frequent than reported, but a large study is needed for confirmation. The condition has a complex physiopathology which can be divided into processes that cause diastolic and/or systolic dysfunction. Diagnosis can be improved by suspecting it in patients with diabetes. There should be a focus on prevention (by tight metabolic control) and, once DCM develops, the objective should be to delay disease progression. ■

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