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Diagnosing diabetic cardiomyopathy

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Abstract: Diabetic cardiomyopathy reflects the presence of structural or functional abnormalities of the myocardium in an individual with diabetes which are not fully explained by other factors known to cause myocardial dysfunction. Diabetes promotes a range of molecular and cellular changes leading to left ventricular concentric hypertrophy, fibrosis, abnormal perfusion, lipid deposition, altered metabolism, diastolic dysfunction, and later progression to systolic dysfunction. Diagnosis of diabetic cardiomyopathy requires identification of such pathological features whilst at the same time excluding other causes of left ventricular dysfunction. In this article, available modalities which can contribute to a diagnosis of diabetic cardiomyopathy are discussed. In most cases a diagnosis of diabetic cardiomyopathy can be reached by echocardiography or cardiac magnetic resonance imaging to detect structural and functional myocardial changes, with computed tomography coronary angiography being employed to exclude obstructive coronary artery disease which could account for left ventricular dysfunction. ■ *Heart Metab*. 2019;80:13-17

Keywords: cardiac computed tomography; cardiac magnetic resonance imaging; coronary artery disease; diabetes; echocardiography; heart failure

Introduction

Heart failure is common in patients with diabetes, with prevalence at least twofold higher in subjects with diabetes than in those without.[1,2] Unrecognized left ventricular dysfunction may affect over one quarter of patients with type 2 diabetes.[3] In some patients with diabetes, left ventricular dysfunction is attributable to other conditions including hypertension or coronary artery disease, but in others diabetes itself is thought to the be the cause.

What is diabetic cardiomyopathy?

The term "Diabetic cardiomyopathy" was first used by Rubler et al in 1972 to describe post-mortem histological findings in hearts from individuals with diabetes and heart failure who did not have coronary artery disease, hypertension, or valvular heart disease.[4] Despite subsequent research to better understand the mechanisms and clinical features of myocardial disease in the presence of diabetes, a consistently applied definition to identify a distinct cardiomyopathic process in diabetes is lacking. Recently Lee et al proposed a pragmatic definition of diabetic cardiomyopathy which will be used here – "cardiac abnormalities not wholly explained by other cardiovascular or non-cardiovascular causes and likely to be due to diabetes."[5]

The factors which underpin myocardial dysfunction in diabetes are described in detail elsewhere in this issue of *Heart & Metabolism*. However, diagnosis is founded on the basis that diabetic cardiomyopathy comprises structural, functional, and molecular alterations which can be assessed using appropriate imaging or biomarkers.[6] At the structural level, diabetes causes increases in left ventricular wall thickness and mass leading to concentric hypertrophy. Diffuse myo-

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cardial fibrosis and deposition of triglycerides lead to expansion of the extracellular matrix. Functional alterations in the early stages of diabetic cardiomyopathy include diastolic dysfunction and altered indices of myocardial deformation, whilst metabolic alterations reflect deposition of lipids and changes in substrate utilization. Over time, diabetic cardiomyopathy is thought to progress to left ventricular dilatation, eccentric remodeling, and systolic dysfunction.[7,8] Some observers, however, believe these "restrictive" and "dilated" phenotypes do not represent successive stages of diabetic cardiomyopathy but evolve independently depending on the type of diabetes and the presence of obesity.[9]

Diagnosis of diabetic cardiomyopathy

A pragmatic approach to diagnosing diabetic cardiomyopathy, summarized in *Figure 1*, first requires identification of structural and functional abnormalities indicative of myocardial dysfunction, and second exclusion of other conditions, in particular obstructive coronary artery disease, which could contribute to impaired cardiac performance. In most cases a diagnosis of cardiomyopathy can be reached by noninvasive cardiac imaging. Exclusion of concomitant obstructive coronary disease can be achieved by coronary imaging with computed tomography or by ruling out ischemia by stress imaging. Roles for circulating biomarkers and assessment of myocardial metabolism are still emerging and not yet in routine clinical use.

There are no universally accepted diagnostic criteria for diabetic cardiomyopathy. In the absence of clinical studies assessing the accuracy of diagnostic techniques specifically in individuals with diabetic cardiomyopathy, diagnosis is reliant on information extrapolated from studies carried out in the broader population with diabetes.

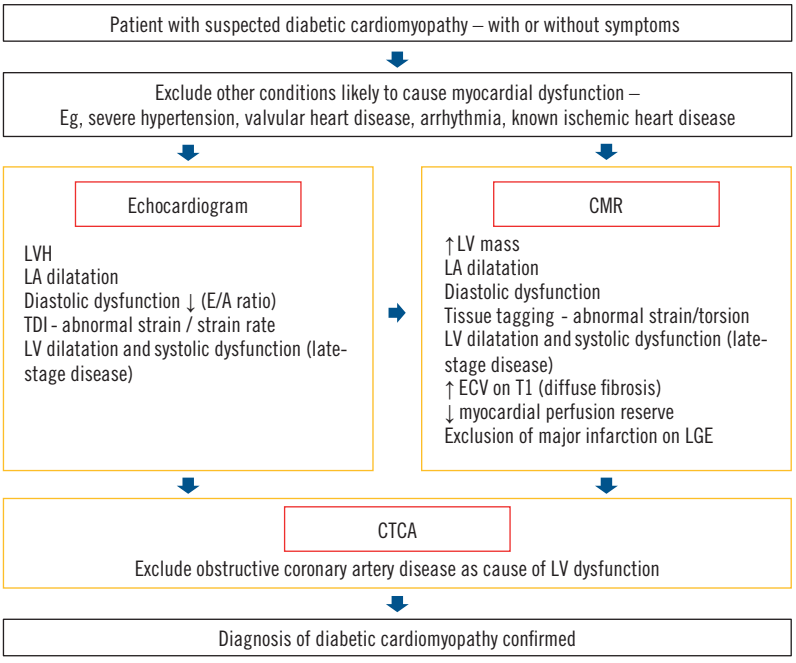

Figure 1 *Proposed algorithm for the diagnosis of diabetic cardiomyopathy. Selection of echocardiography or CMR is dependent on local resource availability. The presence of concentric left ventricular hypertrophy and diastolic dysfunction are characteristic of early-stage disease. Abnormal strain indices, including reduced longitudinal contractility and impaired systolic circumferential strain, are common in diabetes-related myocardial dysfunction. In established diabetic cardiomyopathy, raised extracellular volume on T1 CMR imaging indicates the presence of diffuse fibrosis. In late-stage disease, left ventricular dilatation and systolic dysfunction may be observed, although it is important to exclude a causative role for hypertension and obstructive coronary disease in such cases. E/A, ratio of E-wave to A-wave velocity on trans-mitral Doppler; ECV, extracellular volume; CMR, cardiovascular magnetic resonance; CTCA, computed tomography coronary angiogram; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; LVH, left ventricular hypertrophy; TDI, tissue Doppler imaging*

Echocardiography

Two-dimensional (2D) Doppler echocardiography is the gold-standard tool to identify structural and functional cardiac abnormalities in the evaluation of patients with suspected myocardial dysfunction. Comprehensive evaluation by conventional echocardiography allows the detection of multiple alterations associated with diabetic cardiomyopathy, including left ventricular hypertrophy, left atrial enlargement, and diastolic or systolic left ventricular dysfunction. Echocardiography also allows the exclusion of cardiac valve disease and assessment of regional left ventricular wall motion abnormalities which may indicate underlying coronary artery disease. Impaired left ventricular relaxation, characteristic of diastolic dysfunction, is identified by alterations in pulse-wave transmitral Doppler which are observed in over 50% of patients with asymptomatic type 2 diabetes and normal left ventricular systolic function.[10] Tissue Doppler imaging (TDI) allows detection of

diastolic dysfunction with increased confidence, especially in people with normal E:A ratio (pseudo-normalized pattern) on transmitral Doppler. Using a combination of transmitral Doppler, Valsalva maneuver, and TDI, diastolic dysfunction was detected in 75% of asymptomatic, normotensive patients with diabetes mellitus.[11] Speckle-tracking to assess mechanical deformation (strain) can detect early changes in patients with diabetes with subclinical disease and correlates with the diabetes duration.[12] In the long term, abnormal longitudinal strain predicts adverse ventricular remodeling and impaired prognosis.[13,14] Stress echocardiography, employing pharmacological or treadmill stress, can exclude significant coronary disease, although this may be confounded in diabetes by the presence of microvascular dysfunction. In patients with known or suspected coronary disease, the prognostic value of stress echocardiography is similar in patients with and without diabetes,[15] although this has not been evaluated in the setting of diabetic cardiomyopathy.

Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance (CMR) imaging delivers higher spatial resolution than echocardiography and provides accurate assessment of cardiac structure, left ventricular mass, and systolic and diastolic function. Effects of diabetes on myocardial perfusion may be assessed both in absolute terms and as myocardial perfusion reserve.[16] Assessment of myocardial deformation by tagged imaging or feature tracking facilitates detection of altered myocardial strain or torsion which develop early in diabetic cardiomyopathy and are associated with abnormal myocardial perfusion reserve.[17] CMR can readily exclude regional myocardial changes, including infarction and inducible myocardial ischemia, which allows ischemic-myocardial dysfunction to be identified. This is important as almost one third of patients with diabetes had CMR evidence of previously unrecognized myocardial infarction in a study of older adults.[18] A major advantage of CMR in diagnosing diabetic cardiomyopathy is its ability to detect diffuse myocardial changes such as fibrosis. Late-gadolinium enhancement can identify focal areas of fibrosis, whereas T1 mapping allows identification of the diffuse myocardial pathology characteristic of diabetic cardiomyopathy. In subjects with diabetes, an increase in extracellular volume on T1 mapping, indicative of extracellular matrix expansion due to myocardial fibrosis, is highly suggestive of later-stage diabetes-related myocardial dysfunction and is associated with increased mortality and heart failure hospitalization.[19] CMR assessment of myocardial structure and function can be further augmented by detection of increased triglyceride deposition (myocardial steatosis) and altered myocardial metabolism by MR spectroscopy.[20,21] Using this approach, subclinical changes in subjects with diabetes have been shown by CMR to include concentric left ventricular (LV) remodeling, higher myocardial triglyceride content, impaired myocardial energetics, and impaired systolic strain.[22]

Cardiac CT

Multislice cardiac computed tomography (CT) provides information on ventricular volumes and ejection fraction, but its greatest utility is in exclusion of obstructive coronary artery which could account for left ventricular dysfunction by CT coronary angiography.[23] Although yet to be investigated in the context of diagnosing diabetic cardiomyopathy, CT coronary angiography is associated with improved clinical outcomes in comparison with functional stress testing in patients with diabetes, suggesting that it should be used more widely in this setting.[24] In subjects with suspected diabetic cardiomyopathy, CT findings should be evaluated together with other imaging modalities (echocardiography or CMR) to allow coronary disease to be interpreted in the context of regional myocardial dysfunction.

Nuclear imaging

Gated single photon-emission computed tomography (SPECT) facilitates the simultaneous evaluation of left ventricular function and myocardial perfusion. SPECT is widely used globally for the assessment of myocardial ischemia and a normal result has a high negative predictive value for cardiac events in patients with diabetes and known or suspected coronary artery disease.[25] However, the low spatial resolution of SPECT limits identification of subendocardial ischemia and reliance on detecting regional difference in perfusion diminishes its utility as a diagnostic test in patients with diabetes, who are more prone to diffuse coronary disease or microvascular dysfunction. Posi-

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tron emission tomography (PET) has the advantage of providing quantitative assessment of myocardial perfusion. Coronary vasodilator dysfunction detected by PET is a powerful predictor of cardiac mortality in patients with diabetes.[26]

Biomarkers

Although a wide range of cardiac biomarkers indicative of myocardial disease has been described in patients with diabetes, none has yet reached clinical use to diagnose diabetic cardiomyopathy. Elevated brain natriuretic peptide (BNP) concentration correlates with left ventricular dysfunction and can be employed to screen asymptomatic individuals[27] but does not discriminate the underlying cause. In contrast, a network analysis of patients with acute heart failure identified a panel of biomarkers which were differentially modified by the presence or absence of diabetes, including markers of inflammation (TNFR-1a, periostin), cardiomyocyte stretch (BNP), angiogenesis (VEGFR, angiogenin), and renal function (NGAL, KIM-1).[28] Further research is needed to identify and validate biomarkers specific for the pathological changes underlying diabetic cardiomyopathy.

Conclusions

The approach to diagnosing diabetic cardiomyopathy in individual cases is likely to depend on the local availability of imaging modalities. Concentric left ventricular remodeling and diastolic dysfunction are characteristic of early-stage diabetes-related myocardial dysfunction, particularly in the presence of reduced longitudinal contractility and impaired systolic circumferential strain on strain imaging. Diffuse fibrosis, resulting in increased extracellular volume on CMR, is suggestive of later-stage disease. With wide availability and its established role as a first-line investigation for suspected left ventricular dysfunction, echocardiography lends itself to most commonly be used to detect diabetic cardiomyopathy. Increasing availability of cardiac CT allows noninvasive coronary angiography to be employed to exclude significant coronary artery disease as a cause of myocardial dysfunction. Where available, CMR is the most powerful diagnostic tool for diabetic cardiomyopathy and allows multiparametric assessment of myocardial morphology, fibrosis, perfusion, and function. ■

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