The Detection of Myocardial Fibrosis
An Opportunity to Reduce Cardiovascular Risk in Patients With Diabetes Mellitus?

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Both type 1 and type 2 diabetes mellitus (DM) are associated with a significant increase in cardiovascular risk. Glycemic control has, unfortunately, not been convincingly shown to reduce cardiovascular risk.1–3 The level at which blood pressure should be controlled also is controversial.4 Thus, there may be a need to focus on new therapeutic targets if we are to reduce cardiovascular risk in patients with either type 1 or type 2 DM. Cardiac and large arteries fibrosis is a frequent occurrence in patients with DM and one of the major factors predisposing to the development of heart failure (HF). Cardiac fibrosis is the consequence of extracellular cardiac matrix remodeling resulting from pathological processes, including ischemia; stretch; inflammation; and specifically in DM, oxidative stress, advanced glycation end products, and several neurohormonal mediators. Cardiac fibrosis may cause myocyte slippage, tissue heterogeneity and dys-synchrony, ventricular dilatation, and contractile dysfunction. Myocardial fibrosis alters myocardial compliance, and associated fibrosis-related large artery stiffness may predispose to diastolic dysfunction and HF with a preserved left ventricular ejection fraction. Cardiac fibrosis also may result in alteration of gap junctions and predispose to arrhythmias and sudden cardiac death.5 Bioimaging and biomarkers of cardiac fibrosis, therefore, may become clinically useful tools, particularly given the potential for cardioprotective and cardio reparative pharmacological strategies.6,7

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Detection of Myocardial Fibrosis by Collagen Biomarkers

The measurement of various serum peptides arising from the metabolism of collagen types I and III, of degradation fragments (carboxy-terminal telopeptide of type I collagen), and of specific metalloproteinases may provide a noninvasive assessment of fibrosis.8–10 A strong correlation exists between changes in serum levels of biomarkers for the turnover of extracellular cardiac matrix proteins and ongoing cardiac remodeling. Diagnostic approaches for diabetic cardiomyopathy and myocardial fibrosis have been reviewed recently by Maya and Villarreal.11 More specifically, early changes in serum markers of extracellular cardiac matrix turnover have been described in patients with uncomplicated type 2 DM.12 Serum carboxy-terminal propeptide of type I procollagen has also been shown to be associated with diastolic dysfunction in patients with early type 2 DM.13 However, the use of these assays to diagnose diabetic cardiomyopathy is still experimental and needs to be validated in large-scale studies.

In this issue of Circulation: Cardiovascular Imaging, Ng et al14 describe their experience using MRI-derived global contrast T1 relaxation times to evaluate myocardial fibrosis in patients with type 1 and 2 DM compared with normal controls. They found that patients with DM had a significantly shortened global enhanced postcontrast myocardial T1 relaxation time compared with controls and that T1 relaxation time was a strong determinant of both systolic and diastolic myocardial dysfunction. Although there was a lack of a significant relationship between T1 relaxation times and echocardiographic determination of left ventricular ejection fraction, a relationship was found between T1 relaxation times with systolic and diastolic myocardial function determined by 2D speckle tracking. However, because of a relatively small number of patients with type 2 DM suitable for evaluation, the authors could not be certain that patients with type 1 and 2 DM had a similar degree of fibrosis, nor could they be certain about the role of coronary artery disease, independent of DM, in the extent of fibrosis in patients with type 2 DM.

In a related article in a previous issue of Circulation: Cardiovascular Imaging, Jellis et al15 used postcontrast-enhanced T1 MRI to evaluate 67 apparently healthy subjects with type 2 DM stratified by the presence or absence of subclinical myocardial dysfunction determined by echocardiography. They also evaluated biomarkers of collagen formation, including procollagen type I, procollagen type III, and the carboxy-terminal propeptide of collagen I as well as insulin sensitivity, vascular stiffness as evaluated by pulse wave velocity, maximal oxygen consumption during exercise, and brain natriuretic peptide levels. They found a significant association between postcontrast T1 relaxation times and echocardiographic determination of diastolic dysfunction. Although they could not detect a significant relationship between postcontrast T1 relaxation times and the collagen biomarkers, there was a significant relationship of procollagen type III and procollagen type I, but not carboxy-terminal propeptide of collagen I, with echocardiographic...
myocardial function. Jellis et al concluded that diffuse myocardial fibrosis may be a contributor to early diabetic cardiomyopathy and that the association among imaging parameters of myocardial fibrosis, metabolic parameters, and procollagen biomarkers supports the hypotheses that myocardial fibrosis in patients with DM is linked to a metabolic derangement mitigated by abnormal glycation end products, which alter extracellular matrix formation and enzymatic activity, and impairs collagen turnover with resultant myocardial stiffness and impaired exercise performance, which is associated with a shortened T1 value. On multivariate analysis, diastolic dysfunction was related to postcontrast T1 values but not to systolic blood pressure, arterial stiffness, pulse wave velocity, or left ventricular mass. There was also no association between procollagen biomarkers and parameters of acute or chronic hypertension, suggesting that myocardial fibrosis in these patients was independent of the presence of hypertension. Of interest was their finding that when subjects were stratified according to diastolic function, there was no difference among groups with respect to the use of antihypertensive agents, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Although these 2 studies point out the potential role of MRI, especially postcontrast T1 imaging, it is clear that we need further information on the natural history of myocardial fibrosis and its detection in patients with DM. For example:

- How early after the diagnosis of DM can myocardial fibrosis be detected? We know that myocardial fibrosis can be detected in patients with obesity before the onset of DM. Should we be evaluating patients with visceral obesity and prediabetes for myocardial fibrosis? Should we wait for evidence of myocardial fibrosis by postcontrast T1 MRI before instituting therapy to prevent its progression, or should we institute therapy before there is evidence of myocardial fibrosis to prevent its development and possibly the development of irreversible myocardial damage? Once myocardial fibrosis occurs, there may be damage to gap junctions, a predisposition to sudden cardiac death, and the development of HF. What is the cost-effectiveness of preventing myocardial fibrosis versus preventing its progression once it has been detected by MRI?
- Does the development and extent of myocardial fibrosis depend on insulin sensitivity, the degree of blood glucose control, or some other metabolic parameters?
- Although myocardial fibrosis in patients with DM in the study by Jellis et al was independent of the presence of hypertensive heart disease, the characteristics and extent of myocardial fibrosis altered by fibrosis in other target organs, such as the kidneys, or by the presence of myocardial ischemia, which is also associated with myocardial fibrosis? How does the presence of comorbid conditions, such as hypertensive heart disease, coronary artery disease, and chronic kidney disease, affect the success of therapeutic strategies to prevent the progression of myocardial fibrosis in patients with DM?
- Which therapeutic strategy will be most effective in preventing the development and progression of myocardial fibrosis in patients with DM? In the study by Jellis et al, the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers did not appear to be effective, which is important because studies have suggested that angiotensin-converting enzyme inhibitors can alter the progression of myocardial fibrosis in patients with hypertensive heart disease. Although none of the patients in the study by Jellis et al were taking a mineralocorticoid receptor antagonist, previous data suggest that a mineralocorticoid receptor antagonist is effective in preventing the progression of myocardial fibrosis in patients with HF, many of whom had DM. Mineralocorticoid receptor antagonists have been shown to be effective in reducing urinary albuminuria in patients with DM and chronic kidney disease; thus, they may play an important role in altering the natural history of patients with DM.
- Do the factors linking myocardial fibrosis to DM differ in patients with type 1 and 2 DM?
- Although the study by Jellis et al suggests that the postcontrast T1 MRI evaluation of myocardial fibrosis is more sensitive than either procollagen I or III it is unfortunate that they did not evaluate the utility of measuring galectin 3 levels, which have been shown to correlate with the presence of myocardial and renal fibrosis and to predict cardiovascular outcomes in patients with HF. Would measurement of galectin 3 levels and other biomarkers, such as miRNA, be as or more sensitive than postcontrast T1 MRI for the detection and evaluation of the extent of myocardial fibrosis? What are the implications for healthcare costs if we begin to systematically detect myocardial fibrosis either by MRI, biomarkers, or their combination in an attempt to prevent its development and progression? Would blood extracellular cardiac matrix biomarkers be more widely applicable and cost-effective when screening patients with DM for the presence of cardiac fibrosis? It is likely that biomarkers may be more appropriate for serial monitoring of the progression of cardiac fibrosis and therapy-induced regression of such fibrosis than MRI.

Although there a number of questions that remain unanswered about the pathophysiology, natural history, detection, prognostic implications, and therapy of myocardial fibrosis in patients with DM, it is clear that early detection of myocardial fibrosis by MRI, as exemplified by the studies of Ng et al, Jellis et al, and other investigators, provides a new opportunity to alter the natural history of DM and to reduce cardiovascular mortality and morbidity. Future studies will be needed to determine whether targeting myocardial fibrosis will be as or more important in altering the natural history of these patients than control of blood glucose or blood pressure. Food and Drug Administration guidelines for the development of new antidiabetic drugs has resulted in many thousands of patients with DM being evaluated in long-term studies to determine their cardiovascular benefits and risks. We should take advantage of this opportunity and incentivize the pharmaceutical industry, diabetologists, cardiologists, and radiologists to work together to further understand the role of myocardial fibrosis in patients with DM. New-onset HF.
should be adjudicated as a specific end point in trials of patients with DM. Finally, a factorial design should be used in some of these trials to test the most effective strategy to prevent the development and progression of myocardial fibrosis in these high-risk patients.

Further studies should investigate the respective role of extracellular cardiac matrix biomarker assays, imaging techniques, and their combined use in the early diagnosis of DM-induced changes in cardiac structure and function and as potential tools for monitoring cardiac fibrosis, detecting patients at risk of developing HF, and assessing the value of antidiabetic therapy and specifically targeted therapy to prevent myocardial and other target organ fibrosis. It will be important, however, to standardize MRI protocols for detecting myocardial fibrosis if we are to take optimum advantage of the studies by Ng et al14 and Jellis et al15 to alter the natural history of patients with DM.

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References

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