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EDITORIAL COMMENT

An MR Spectroscopy-Based Approach to Lean Versus Obese Diabetic Patients*

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Obesity is 1 of the strongest single predictors for the development of insulin resistance and type 2 diabetes (T2D). Remarkably, the incidence of obesity has doubled in the world population since 1980, as the World Health Organization numbers 1.9 billion adults as overweight, including >600 million obese people in 2015, reflecting the still growing significance of this widespread condition and of the appropriate assessment of concomitant diseases (1). Both obesity and T2D are associated with nonalcoholic fatty liver disease and increased cardiovascular risk (2,3). Importantly, the observation that diabetic cardiomyopathy does not only occur in obese but also in many lean T2D patients suggests the presence of different mechanisms resulting in cardiac disease in T2D patients (4). In this context, visceral and ectopic fat stores with specific systematic and/or regional effects seem to carry a greater cardiovascular risk than total fat accumulation (5-7).

SEE PAGE 53

In this issue of *Journal*, Levelt et al. (4) address an interesting clinical question that may have important future implications for a large group of patients: Does the presence of ectopic and visceral fat deposition in diabetic patients lead to a pathological cardiovascular phenotype—even in the absence of a global increase in total body fat? The study results include some good news and some bad news for patients with T2D. The good news is that physicians are able to detect even subtle metabolic abnormalities in the heart muscle "noninvasively." The bad news is that not only "obese" (Ob) but also "lean" (Ln) T2D patients already show metabolic abnormalities in the myocardium, even in the absence of functional cardiac abnormalities.

By the use of a very comprehensive methodological approach—comprising: 1) cardiac computed tomography imaging; 2) multiparametric cardiovascular magnetic resonance imaging (MRI), including myocardial spectroscopy; and 3) multiparametric liver MRI in both Ob and Ln T2D patients (and healthy control subjects)—Levelt et al. (4) were able to study some highly interesting associations between the extent and distribution of ectopic/visceral fat and the presence of structural changes in the liver and of structural, functional, and energetic changes in the heart.

Metabolic liver analyses suggested the presence of hepatic steatosis in both Ob-T2D and Ln-T2D; however, a higher degree was seen in Ob-T2D. In contrast, iron-corrected T_1—an MRI parameter reflecting fibroinflammatory changes in the liver (8)—was only elevated in Ob-T2D compared with Ln-T2D and control subjects. Interestingly, these MRI-based observations (presence of hepatic steatosis and/or fibroinflammatory changes) were not accompanied by elevated serum liver enzymes. Hence, noninvasive MRI enabled the detection of structural liver abnormalities that could not be depicted with simple serum enzyme tests. Consequently, such MRI-based analyses may help to identify those T2D patients that are more likely to experience or may develop nonalcoholic fatty liver disease—an important cause of death in patients with T2D—as well as nonalcoholic steatohepatitis (9,10).

Furthermore, MRI-based assessment of left and right ventricular systolic function did not result in any differences between the groups. However,

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myocardial circumferential strain analysis showed impaired peak circumferential systolic and diastolic strain rates (evaluated using tagged magnetic resonance [MR] images) in Ob-T2D compared with both healthy control subjects and Ln-T2D. Such subtle "functional cardiac abnormalities" were only detected in Ob-T2D, but not in Ln-T2D. Additional metabolic cardiac analyses (on the basis of ^{1}H- and ^{31}P-MR spectroscopy) revealed the presence of "cardiac steatosis" as well as myocardial energy deficits not only in Ob-T2D but also in Ln-T2D compared with control subjects; however, there were no relevant differences between Ob- and Ln-T2D despite higher epicardial fat volumes (measured by cardiac computed tomography) in Ob-T2D compared with Ln-T2D. These findings deserve attention because they suggest the occurrence of metabolic changes that can be measured and quantified by noninvasive MRI-based spectroscopy, even in Ln-T2D and prior to (or independent from?) the manifestation of "functional" abnormalities.

From a pathophysiological point of view, there are several challenging questions regarding the complex relationship between the occurrence of insulin resistance and/or epicardial fat in T2D patients and the manifestation of diabetic cardiomyopathy:

1. How does increased insulin resistance affect the degree of epicardial fat (and vice versa) and cardiac involvement in T2D?
2. What effect does epicardial fat really have on the function and structure of the myocardium, particularly in Ln-T2D?
3. Does the aforementioned finding of cardiac steatosis as well as myocardial energy deficits in Ln-T2D—which did show less epicardial fat than Ob-T2D—suggest a different pathomechanism of cardiac involvement that is not driven by the degree of epicardial fat?
4. Will these findings help us unravel the complex pathophysiology of diabetic cardiomyopathy and allow the implementation of novel therapeutic strategies at a very early stage of cardiac involvement?

The authors also performed correlation analysis regarding potential associations between the degree of insulin resistance and their imaging findings. It is noteworthy that they found some correlation of cardiac strain parameters with hepatic and epicardial fat and insulin resistance. However, although some statistically significant relationships were detected, a substantial association was not shown, and causal relationships cannot be deduced from the presented correlation analyses in a rather small study group. Moreover, the authors did not assess serum catecholamine or adiponectin levels, which would help clarify the association between epicardial fat and imaging findings of diabetic cardiomyopathy.

Obviously, this was a descriptive observational study without evidence of mechanistic or time-dependent causality. Therefore, we are not yet able to answer the aforementioned questions. However, the intriguing diversity and specificity of the noninvasive data that can be obtained, particularly by multiparametric MRI (including MR spectroscopy)—nicely and convincingly illustrated by the authors of this study—opens up new vistas in the accurate diagnosis and (serial) monitoring of both cardiac and liver diseases (not only in T2D patients). Such comprehensive imaging approaches in the context of well-designed longitudinal interventional and/or therapeutic studies will play an important future role in exploring causal relationships of, for example, diabetic cardiomyopathy in humans without putting the respective individuals at any relevant additional invasive/diagnostic risk. After almost 2 decades of research in MR spectroscopy (11–13), the time seems ripe for a wider clinical use of this technique, not only in T2D patients and not only for studying the human heart.

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