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EDITORIAL COMMENT

From Metabolic Exposome to Onset of Diabetic Cardiomyopathy*

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The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide, and this diabetes epidemic is afflicting all ages, both sexes, and all socioeconomic classes, leading to frailty and compromising healthy aging. Although there has been an increase in lifespan, these gains are offset by obesogenic conditions and glycemic dysregulation, which are expected to be the major contributors to cardiovascular mortality and morbidity in the 21st century. The Framingham study, which investigated a cohort of 5,209 diabetic men and women aged 30 to 62 years, reported an increased incidence of annual cardiovascular death in this population (1). In addition to T2DM, other disorders of glucose metabolism are also risk factors, as evidenced by the collaborative DECODE study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe), which showed increased mortality in patients with T2DM and impaired glucose tolerance (IGT) but not in those with impaired fasting glucose (IFG) (2).

One of the major clinical events among these cardiovascular diseases in people with diabetes mellitus is the onset of cardiomyopathy, originally described as heart failure occurring in the absence of hypertension, coronary artery disease, and valvular or congenital heart disease. Diabetic cardiomyopathy is now recognized as a distinct disease that leads to ventricular hypertrophy and abnormal myocardial contractility, which correlate with multifactorial and complex molecular and cellular changes. Indeed, both insulin resistance and chronic hyperglycemia contribute to impair cardiac contractility and structure via reduced Ca^{2+} influx through L-type Ca^{2+} channels, impairment of the phosphatidylinositol 3-kinase/Akt pathway, reactive oxygen species accumulation, increased formation of advanced glycation end products, production of fatty acid metabolites (e.g., ceramides), and multiple potential mechanisms such as autophagy, microRNAs, and epigenetic mechanisms (3).

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In this issue of *iJACC*, the cross-sectional study based on the CARDIA (Coronary Artery Risk Development in Young Adults) cohort adds an important piece of evidence about the toxicity of glycemic dysregulation by exploring how long-term exposure to glycemic abnormality and insulin resistance contributes to cardiac dysfunction and remodeling in mid adulthood (4). The authors examined CARDIA cohort participants at year 25 and categorized them into 4 groups: those with normal glucose tolerance, IFG or IGT, T2DM for >10 years, and T2DM for <10 years. The major finding of this study is that there is an association between the severity of the glycemic status or insulin resistance, the duration of glycemic disorders, and the prevalence of cardiac abnormalities (left ventricular [LV] hypertrophy, LV systolic and diastolic dysfunction).

Regarding myocardial dysfunction, the prevalence of systolic abnormalities when evaluated by LV longitudinal systolic strain was higher than the prevalence of diastolic dysfunction as assessed by the E/e′ ratio in the 3 groups with glycemic abnormalities (IFG or IGT, T2DM for >10 years, and T2DM for <10 years) compared with euglycemic subjects. This finding is quite interesting in light of the existing controversy as to whether diastolic dysfunction is the earliest manifestation of diabetic cardiomyopathy and how specifically it is affected by glycemic disorders, among a number of other confounders (5). Moreover, longitudinal systolic strain was able to unmask subtle

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systolic abnormalities in the groups with early and late onset of T2DM and IGT/IFG, which is in line with recent echocardiographic and magnetic resonance imaging studies demonstrating that patients with T2DM exhibit decreased LV systolic strain compared with euglycemic subjects and with speculation that such an abnormality could be considered an early marker of diabetic cardiomyopathy (6,7). Thus, this large cohort study confirms initial observations in smaller populations that indicate that subclinical LV systolic dysfunction is frequently observed in asymptomatic patients with diabetes mellitus with normal LV ejection fraction and that the decrease in LV longitudinal systolic strain is independently associated with duration of diabetes mellitus (6). This study also brings an additional argument for the progressive deterioration of systolic and diastolic function in a time-dependent fashion together with poor glucose control. It extends the findings of longitudinal studies that reported after 2-year follow-up a progression of subclinical dysfunction, with further impairment in LV longitudinal and circumferential systolic strain and a reduction in early diastolic strain rate together with an increase in LV mass but no change in conventional echocardiographic measurement of LV systolic and diastolic function (8).

Regarding myocardial remodeling, the CARDIA investigators also demonstrate that both T2DM and high insulin resistance significantly impact LV remodeling with LV hypertrophy and increased relative wall thickness. Again, these results are consistent with large cohort studies that have underlined the influence of diabetes mellitus on cardiac LV remodeling over a lifetime (9,10). Although the aging process is associated with a progressive increase in LV wall thickness and a decrease in LV cavity dimensions in healthy people, the presence of diabetes mellitus induces a more pronounced increase in LV wall thickness but the absence of a proportional decrease in cavity dimensions (9). Therefore, the CARDIA cross-sectional study suggests that the progression from glucometabolic disorders to overt ventricular dysfunction begins with subclinical dysfunction. Previous longitudinal studies have investigated the potential impact of these subtle abnormalities on the evolution of LV function and LV geometry and have demonstrated the association between abnormal systolic strain in patients with diabetes mellitus and cardiac remodeling over time (11) and, more recently, with clinical adverse events, including heart failure and death (12). This underlines the interest in unmasking subclinical systolic dysfunction by use of longitudinal strain to predict subtle LV remodeling that could progressively lead to heart failure after a long silent phase.

However, both hypertension and obesity (body mass index >30 kg/m^2) were more prevalent in diabetic groups than in euglycemic and IGT/IFG groups. The obvious question that these results raise is that of the respective role of the different confounders on the cardiac changes observed. The frequent coexistence of hypertension, obesity, and T2DM makes the contribution of the glucometabolic state to the myocardial dysfunction difficult to isolate, and it is debatable whether the myocardial dysfunction is triggered by the glucometabolic disorder itself rather than the synergistic action of these factors.

This report from the CARDIA study provides strong evidence for the diagnosis of diabetic cardiomyopathy and demonstrates that subtle systolic or diastolic myocardial abnormalities occur early in its development and precede the onset of overt cardiomyopathy. Future research should evaluate the respective role of the metabolic exposome, including dietary lifestyle, glycemic disorders, obesity, and sedentarity, among other potential confounders such as systemic hypertension and aging, which are intertwined in the pathogenesis of "metabolic" cardiomyopathy.

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