Relation of Early and Late Stages of Glucose Metabolism Disturbances With Left Ventricular Geometry and Function
Are Sugar Kisses Bad for the Heart?

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Type 2 diabetes mellitus (T2DM) is the most frequent metabolic disease and is a major risk factor for cardiovascular diseases and mortality. About 9% of the worldwide population, around 347 million people, is expected to present this condition with 50% to 80% of them having a future fatal cardiovascular complication like myocardial infarction, stroke, or heart failure.\(^1\) Even more concerning, estimations from the National Health and Nutrition Examination Survey demonstrated that ≤35.3% of the adult US population has prediabetes.\(^2\) This is 4 times the number of subjects currently having already a diagnosis of T2DM.\(^3\) However, not much is known about the preclinical cardiovascular changes, such as alterations of left ventricular (LV) structure and function, associated with dysglycemic conditions before the diagnosis of T2DM.

The study by Demmer et al\(^4\) in this issue of *Circulation: Cardiovascular Imaging* investigated the associations of 3 primary exposures (glycemic status, diabetes mellitus control, and insulin resistance as assessed by homeostasis model assessment-estimated insulin resistance quintiles) with cardiac structure and function by modern echocardiographic techniques. Although the diabetes mellitus status was based on American Diabetes Association criteria, the definitions were a little mixed with the use of glycohemoglobin (HbA1c), fasting plasma glucose, and 2-hour postload plasma glucose. The agreement among fasting plasma glucose, 2-hour postload plasma glucose, and HbA1c for the definition of groups of nondiabetic, prediabetic, and diabetic is not perfect, and the agreement between fasting plasma glucose, 2-hour postload plasma glucose, and HbA1c for the definition of groups of nondiabetic, prediabetic, and diabetic is not perfect, and individuals included in each group are expected to be different depending on the test used.\(^4\) Accordingly, a more preferable approach would be the use of just one definition. The study sample consisted of 1818 individuals (57% women) aged >45 years (average age: 56 years) with Hispanic/Latino ethnicity (predominant self-identifying background was Mexican with 25% of the total sample), which were participants of the ECHO-SOL study (Echocardiographic Ancillary Study to the Hispanic Community Health Study/Study of Latinos). There was a notable high prevalence of diabetes mellitus of 28% (53% of these individuals had controlled HbA1c levels <7.0%, and 47% an uncontrolled diabetes mellitus with HbA1c levels ≥7.0%) and a high proportion of 42% of individuals presenting with prediabetes. Accordingly, 70% of the study participants were exposed to some degree of a dysglycemic state; hence, this is a real high-risk sample.

Diabetes mellitus has been associated with a plethora of cardiovascular morbidities such as a higher prevalence of atherosclerosis in major arteries and in the coronary bed leading to myocardial infarction, stroke, and peripheral artery disease. Adding to these complications, microangiopathic alterations play also a key role that may result in retinopathy and renal dysfunction.\(^5\) Although diabetes mellitus, through hypertension and atherosclerosis, leads to LV remodeling, its direct effects on LV geometry and function are not yet completely understood. This condition, called diabetic cardiomyopathy, was first recognized >40 years ago.\(^6\) Animal models of diabetic cardiomyopathy showed pathophysiological changes in myocardial structure, calcium signaling, and metabolic pathways that might lead to clinical cardiac dysfunction.\(^7\) The characterization of diabetic cardiomyopathy involves the presence of an impaired glucose metabolism and the exclusion of other possible conditions such as coronary, valvular, hypertensive, or congenital heart disease or a cardiomyopathy occasioned by virus, toxic agents, genetic traits, or infiltration.\(^8\)

Although the diabetic cardiomyopathy was first defined as a dilated cardiomyopathy type disorder characterized by eccentric LV hypertrophy and systolic dysfunction, more recent studies showed a predominant concentric remodeling accompanied by diastolic dysfunction. Both clinical presentations seem to be potential complications of diabetes mellitus leading to heart failure with preserved LV ejection fraction or reduced LV ejection fraction.\(^9\) The presence of insulin resistance (in combination with hyperinsulinemia), hyperglycemia, lipotoxicity, and oxidative stress, usually prevalent in obese patients with T2DM, seems to lead to a coronary microvascular endothelial dysfunction that results in a restrictive type of heart failure with preserved LV ejection fraction. On the contrary, the presence of cardiomyocyte cell death, usually more prevalent in patients with type 1 diabetes mellitus.
with an increased autoimmune response, seems to result in a dilated form of heart failure with reduced ejection fraction. Additionally, coronary microvascular rarefaction and deposition of advanced glycation end products are associated with both clinical presentations.5

The results from Demmer et al suggest that, in their sample of Hispanic/Latino individuals, the presence of glucose dysregulation and insulin resistance were predominantly associated with a concentric remodeling of the left ventricle accompanied by greater ventricular stiffness and impaired diastolic function, all characteristics of the clinical entity of heart failure with preserved LV ejection fraction.

Previous reports from the Framingham Heart Study,6 SHS (The Strong Heart Study),10 MESA (The Multiethnic Study of Atherosclerosis),11 and the MONICA/KORA study (Monitoring Trends and Determinations in Cardiovascular Diseases/Cooperative Research in the Region of Augsburg)12 showed associations of diagnosed diabetes mellitus with higher LV wall thickness and mass, well-known risk factors for mortality and heart failure.13 The present study, in concordance with a recent study,13 demonstrated that also glucose intolerance and insulin resistance were associated with an increase of LV posterior, interventricular septal, and relative wall thickness and higher LV mass. The cardiac hypertrophy might be the result of increased cytokines, like leptin (through endothelin 1-mediated reactive oxygen species production) and resistin (by IRS-1 and MAPK signaling pathways), formed by the adipose tissue of obese individuals or even a direct effect of hyperinsulinemia acting as a growth factor in the heart.7,14

Besides the effects on the LV geometry, former reports15–17 demonstrated a clear effect of diabetes mellitus on LV diastolic dysfunction. The present study, in line with another previous study,18 also showed that glucose intolerance and insulin resistance were associated with a reduction in the peak e’ velocity (resulting in an increased E/e’ ratio). This impairment of diastolic function seems to be the result of a LV concentric remodeling (including fibrosis that followed myocytes apoptosis), a decreased coronary flow reserve (as a consequence of an endothelial and microvascular dysfunction induced by hyperglycemia and insulin resistance), a sympathetic overdrive, and an impaired cardiac homeostasis metabolism and fatty acid metabolism (with resultant myocardial triglyceride accumulation, increased cardiac oxygen consumption, and mitochondrial dysfunction).7,8,19

The finding of an impaired systolic LV function, as determined by LV ejection fraction, accompanying increased levels of HbA1c is a little controversial. Although previous cross-sectional analyses from the Framingham Heart Study20 and ARIC (The Atherosclerosis Risk in Communities Study)21 did not find a relation between diabetes mellitus and LV ejection fraction, the longitudinal MONICA/KORA study22 showed that individuals who have been diagnosed with diabetes mellitus 10 or more years ago had a decreased LV ejection fraction when compared with nondiabetic subjects. Eventually, more refined echocardiographic techniques, for the measurement of the systolic LV function, might provide further clarification for this question.

Taken together, the results of the present study suggest that the chances for the development of diabetic cardiomyopathy result from a continuous exposure to a dysglycemic condition, characterized by hyperglycemia and insulin resistance, rather than a dichotomy categorization of diabetes mellitus versus nondiabetes. Moreover, it shows that echocardiographically detectable abnormalities occur even before the diagnosis of T2DM, indicating the possibility of suitable interventions in the presence of early indicators of glucose intolerance.

**Future Directions**

The actual approach for prevention of cardiovascular impairment after diabetes mellitus and other dysglycemic conditions (including prediabetes and insulin resistance) can be resumed as: too little, too late.

We need global prevention strategies for primary and secondary complications and for related comorbidities and risk factors such as increased body mass index, blood pressure, and cholesterol levels. The discovery of new biomarkers and the development of more precise imaging diagnosis by echocardiography and other techniques like magnetic resonance imaging might facilitate earlier detection, risk stratification, and nonpharmacological and pharmacological treatment of cardiac complications related with dysglycemic complications. Besides, because there is better understanding of the molecular and pathophysiological mechanisms that predispose the diabetic heart to develop heart failure, new therapies might help to alleviate the burden of prediabetes and diabetes mellitus on the heart. Although the nonpharmacological treatment goals of prediabetes and T2DM are comparable, like lifestyle interventions, the pharmacological ones (together with associated disorders such as hypertension and dyslipidemias) and the selection of medications are not. Future studies might clarify whether a pharmacological treatment of early stages of insulin resistance and prediabetes (eg, with the use of new insulin-sensitizing agents) might avoid myocardial and microvascular alterations of the heart and ultimately might have positive effects on cardiovascular morbidity and mortality.

**Disclosures**

None.

**References**

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