Making sense of subclinical cardiac alterations in patients with diabetes

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Patients with diabetes are prone to develop a distinct primary myocardial condition, diabetic cardiomyopathy, placing them at an increased risk for heart failure [1-3]. This occurs independently of hypertension, coronary artery disease, and other established causes of heart failure. Pertinent findings include increased mass, concentric changes, and diastolic dysfunction of the left ventricle [4,5]. Such adverse remodeling is common among patients with diabetes and appears to be strongly associated with its duration, suggesting a role for persistent metabolic stress [6-8]. However, which exact components of the diabetic syndrome determine these cardiac alterations is not clear. Moreover, most studies have investigated patients with type 2 diabetes, and it is uncertain whether patients with type 1 diabetes experience similar myocardial changes.

In keeping with this knowledge gap, the recently published study by Šuran et al. examined cross-sectional associations between markers of left ventricular structure and function and easily obtained anthropometric and laboratory variables, among patients with type 1 diabetes [9]. Sixty-one study participants with a mean age of 34 years and mean body mass index 27 kg/m², without manifest cardiovascular disease or hypertension, and with a duration of diabetes >5 years (mean 18 years) were consecutively included. Patients with chronic kidney disease stage ≥G2 or gross echocardiographic abnormalities were excluded. The investigators found body mass index to be moderately correlated with various markers of cardiac structure and diastolic function (Figure 1). Body mass index remained significantly associated with left ventricular mass, left atrial volume, left ventricular end-diastolic diameter, and E/A after accounting for age, diabetes duration, and average glycated hemoglobin (HbA1c) during the last 5 years. On the other hand, variables like fasting serum glucose, diabetes duration, and HbA1c did not, for the most part, demonstrate relations with echocardiographic measures. The authors concluded that overweight and obese patients with type 1 diabetes may be particularly prone to developing cardiomyopathy.

While the lack of robust associations between glycemic abnormalities and adverse left ventricular remodeling may be unexpected, results regarding this relationship have not been entirely consistent and appear to depend on the characteristics of the study participants. For example, a cross-sectional study of 693 apparently healthy individuals (median age 66 years) derived from the Swedish Malmö Preventive Project found body mass index, but not fasting plasma glucose, to be linked with left ventricular mass and left ventricular hypertrophy [10]. Body mass index was not associated with diastolic function, although that may have been caused by the inclusion of left ventricular mass index in the multivariable analyses [11]. In a subgroup of 247 men (median age 47 years), body mass index was an independent predictor of future left ventricular mass and diastolic function, while insulin sensitivity was not [12]. Curiously, a Japanese cross-sectional study of 145 patients with type 2 diabetes who were matched with 90 healthy controls showed that body mass index ≥25 kg/m² only predicted lower global longitudinal strain among those with diabetes [13,14]. Still, HbA1c was not independently associated with global longitudinal strain.

A proper discussion of type 1 diabetes inevitably requires mention of the Danish Thousand & 1 study [15]. Jensen et al. examined 1093 patients with type 1 diabetes (mean age 50 years) without known heart disease and with a mean diabetes duration of 25.5 years, 15.5% of whom displayed grossly abnormal systolic or diastolic findings. In the primary report, diabetes duration was significantly associated with echocardiographic alterations [15]. In contrast, HbA1c was not associated with a pathological echocardiogram, but albuminuria, whether of the micro or macro subtype, was a powerful predictor...
thereof. Individual Doppler-echocardiographic indices of diastolic function were impaired among patients with diabetes versus those without, regardless of albuminuria [16], though remarkably, global longitudinal strain only differed from healthy controls among those with albuminuria [17]. Accordingly, a fair portion of the heterogeneity between studies could also be attributed to the specific echocardiographic measures that are tested, particularly since they may display complex, non-linear associations with actual myocardial function [18,19].

Finally, the different phenotypes within each diabetic entity may limit direct comparisons [20]. In other words, type 2 diabetes is not just type 2 diabetes, and type 1 diabetes is not simply type 1 diabetes as exemplified by the Thousand & 1 study. Insulin resistance, hyperinsulinemia, obesity, hypertension, and diabetes also frequently co-occur, making it difficult to assess the separate role of each of these conditions in developing structural and functional cardiac alterations [21-23]. However, as Šuran et al. also suggested, hyperglycemia may primarily exert its effects by increasing the susceptibility of the heart to other adverse stimuli [9]. This complies with the classical concept of a cardiovascular continuum, whereby both physiological aging and pathological aging due to cardiovascular risk factors such as diabetes result in similar disturbances in left ventricular structure and function [24-26]. Indeed, in the Thousand & 1 study, those with diabetes developed adverse echocardiographic changes at a much earlier age than would otherwise be expected [16]. As such, hyperglycemia may also modify the relationship between body mass index and cardiovascular disease. Adding to this the fact that post-load glucose may better predict cardiovascular morbidity and mortality than fasting glucose [27], one may have a possible explanation of why body mass index appears to be more consistently associated with abnormal echocardiography than do fasting glucose and HbA1c [28]. Other, simpler explanations for the lack of associations in the present, hypothesis-generating study may include the study participant homogeneity, including the exclusion of patients with known cardiovascular disease, and limited sample size (type 2 error). Additionally, the apparent associations with body mass index might have been exaggerated by the fact that, for these particular analyses, the echocardiographic variables were not indexed for body surface area or allometrically scaled, e.g., by height [29].

In conclusion, the findings reported by Suran et al. are thought-provoking and add to the notion that optimal treatment of patients with diabetes and subclinical cardiac damage may require targeting of multiple, interrelated pathways. Future studies should focus on whether weight loss and non-insulin therapy, e.g., sodium-glucose cotransporter-2 inhibitors, among patients with type 1 diabetes and overweight or obesity may improve myocardial function [29,30]. Lastly, it remains to be determined how these patients should be monitored and whether particular subgroups may benefit from echocardiographic surveillance.

DECLARATION OF INTERESTS

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