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Could hyperglycemia-induced cardiac autoimmunity be hidden behind cardiovascular disease in type 1 diabetes mellitus?

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Type 1 Diabetes Mellitus (T1DM) is considered an autoimmune disorder triggered by dysfunctional adaptive immune responses, mainly of T-cell mediated mechanism, to the insulin-producing β cells in the pancreas. Nevertheless, the presence of multiple islet autoantibodies (≥2), rather than a specific antibody, is thought to be most predictive of progression to overt T1DM [1]. According to studies observing infants with multiple autoantibodies present, risk of appearance of clinical diabetes at 5, 10, and 15 years has been estimated to be 44%, 70%, and 84%, approximately [2]. Data from TrialNet, which has evaluated more than 180,000 relatives of participants with T1DM confirmed the extremely high risk of T1DM among relatives with multiple autoantibodies. In particular, the rate of progression from the presence of multiple autoantibodies to clinically overt diabetes has been estimated to be between 10% and 12% per year [3,4]. For those with clinically overt disease, preservation of C-peptide has been associated with better glycemic control and fewer complications. Indeed, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study has demonstrated that aggressive glucose control results in long-term benefits, such as the reduction of micro/macrovascular complications [5]. Thus, in this context, even short-term preservation of C-peptide seems beneficial [6,7].

T1DM patients with poor glycemic control exhibit a >10-fold elevated risk of morbidity and mortality from cardiovascular disease (CVD) compared to the general population, without sharing conventional CVD risk factors with patients suffering from DM type 2 (T2DM) [8]. Although data have shown that hyperglycemia is the key link to CVD events and associated mortality in T1DM, a very recent study by Sousa et al in *Circulation* reveals a potential novel mechanistic connection between hyperglycemia and CVD in T1DM [9]. Sousa et al sought to estimate the prevalence and profiles of cardiac autoantibodies in longitudinal samples from the DCCT among subjects with glycated hemoglobin (HbA1c) ≥9.0% (n=83) and ≤7.0% (n=83). They evaluated coronary artery calcification in the post-DCCT EDIC Study, high-sensitivity C-reactive protein (measured during EDIC years 4 to 6), and CVD events (defined as stroke, nonfatal myocardial infarction, death resulting from CVD, heart failure, or coronary artery bypass graft) over a 26-year median follow up [9]. Because of the unavailability of peripheral blood mononuclear cells to determine individual $CD4^+$ T-cell populations, the levels of a panel of five cardiac muscle-specific autoantibodies (directed to myosin heavy chain 6, myosin heavy chain 7 and cardiac troponin/cTnI) were measured. The same panel of cardiac autoantibodies was also determined: 1) in matched patients with T2DM with HbA1c ≥ 9.0% (n=70) and ≤7.0% (n=140); 2) in patients with chronic Chagas cardiomyopathy who served as controls (n=51); and 3) in healthy control subjects (n=115) [9]. The key summarized findings of the study are the following: 1) Poor glycemic control, as evidenced by the elevated HbA1c levels, in T1DM patients, was linked to cardiac autoimmunity, as shown by the presence of ≥2 cardiac autoantibody types; 2) The presence of ≥2 cardiac autoantibodies was related to increased risk of CVD events as well as coronary artery calcification later in life; 3) Positivity for ≥2 autoantibodies identified patients with T1DM and increased serum high-sensitivity C-reactive protein (hsCRP) levels, suggesting that cardiac autoimmunity is related with a subclinical inflammatory state, that may be the link between cardiac autoantibodies and CVD outcomes. On the contrary, poor glycemic control was not related to cardiac autoimmunity among patients with T2DM, providing a novel CVD pathogenetic pathway specific to T1DM [9]. Overall, based on the study by Sousa et al, it seems that hyperglycemia-induced subclinical myocardial injury in patients with T1DM, characterized by a dysfunctional immune tolerance, may trigger cardiac autoimmunity in the form of autoreactive T-cell response and production of cardiac myosin-specific autoantibodies, leading to a subclinical myocarditis with many similarities to Chagas disease caused by the protist *Trypanosoma cruzi*, and a subsequent pro-inflammatory state, characterized by elevated hsCRP, and increased risk of atherosclerotic vascular disease and CDV events as shown in Fig. 1 [9–11].

Despite its limitations regarding mainly the small number of CVD events and the non-determination of $CD4^+$ T-cell responses to cardiac myosin, this intriguing study by Sousa et al. may have many important implications in prevention, risk stratification, early diagnosis and, probably, in therapeutic options among patients with T1DM. If validated in larger prospective studies, cardiac autoantibodies could be used as prognostic and predictive biomarkers of CVD in T1DM patients, stratifying patients for CVD risk. The TrialNet abatacept (CTLA4-Ig) in recently-onset T1DM demonstrated that after 2 years of treatment, this agent was associated with 59% more C-peptide secretion compared with placebo and that C-peptide levels remained higher in the treated group 1 year after cessation of treatment [12]. Also, the agent rituximab (anti-CD20)

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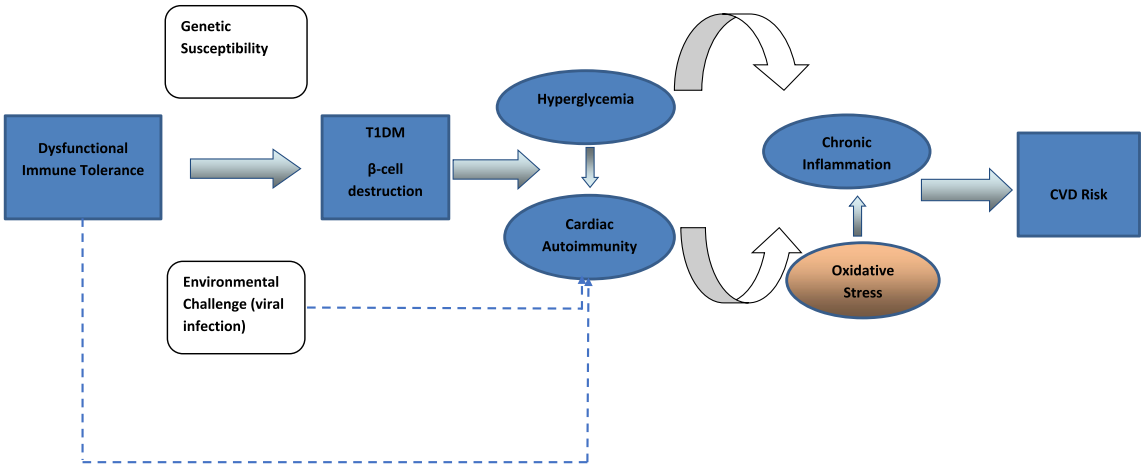

Fig. 1. Potential mechanisms of how hyperglycemia and cardiac autoimmunity are related with excess risk of cardiovascular disease (CVD) in type 1 diabetes mellitus (T1DM) patients.

slowed decline in stimulated C-peptide and was associated with lower insulin requirements and HbA1c levels over 12 months in patients with recently-onset T1DM [13]. It is important to note that rituximab was given only as a single course of drug in this study, in marked contrast to the way the drug is used in clinical practice for other autoimmune diseases. Thus, immunotherapy seems to "work" in T1DM just as effectively as it "works" in other autoimmune diseases [12]. Therefore, immunotherapy targeting cardiac auto-immunity improving the burden of CVD and its outcomes among patients with T1DM might be of great interest and potential in the near future.

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