Is β-Cell Dysfunction Present in Adult Autoantibody Negative Relatives of Individuals with Type 1 Diabetes Mellitus?

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Background/Objective: Individuals with a family history of type 1 diabetes mellitus (T1D) are at increased genetic risk for T1D. Previous studies identified the presence of β-cell dysfunction before clinical onset and diagnosis of T1D. However, it is unclear if β-cell dysfunction predates islet autoimmunity in individuals at high genetic risk. Our objective was to test β-cell function in islet antibody negative adults who have a first-degree relative with T1D. We hypothesized that individuals at genetic risk for T1D would exhibit β-cell dysfunction even without detectable islet autoimmunity.
Methods: We used ordinary one-way and Brown-Forsythe ANOVA to compare the repeated mixed meal tolerance test (MMTT) and hyperglycemic clamp glucose-stimulated β-cell response and function measures between three groups of individuals: normoglycemic adults without T1D family history age, sex, and BMI-matched islet antibody negative first-degree relatives of individuals with T1D, and islet antibody positive first-degree relatives of individuals with T1D.
Results: Neither the MMTT first-phase insulin secretion measures (c-peptide$_{0\text{-}15\ minutes}$, c-peptide$_{0\text{-}30\ minutes}$, insulin$_{0\text{-}15\ minutes}$, insulin$_{0\text{-}30\ minutes}$), nor second-phase measures (c-peptide$_{0\text{-}120\ minutes}$, insulin$_{0\text{-}120\ minutes}$, and glucose$_{0\text{-}120\ minutes}$) showed a statistically significant difference between groups. The clamp acute c-peptide response to glucose, insulin sensitivity, c-peptide steady state, first-phase β-cell function, and second-phase β-cell function were similar between subject groups in both visits. Fasting proinsulin:c-peptide ratios, a biomarker of β-cell stress, were also similar between participant groups.
Conclusion and Impact: Our data suggest that genetically at-risk autoantibody negative adult relatives of individuals with T1D do not demonstrate β-cell dysfunction compared to controls. Studies show that β-cell ER dysfunction preceding T1D onset is more striking in younger children. Thus, our findings may reflect the use of an adult study population. Alternatively, β-cell dysfunction in T1D may require initial autoimmune activation. This study will contribute to the growing understanding of risk factors contributing to T1D development.

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