

## **Residual Beta Cells in Autoimmune Type 1 Diabetes Mellitus**

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Purpose: Autoimmune Type 1 diabetes is a disease characterized by chronic beta cell loss which continues after onset and positivity for anti-islet autoantibodies. Given the insulin dependence typical of patients with autoimmune diabetes, it is generally believed that there is little or no residual beta cell mass in patients with long standing disease. Previous reports have however shown that amongst patients with childhood diabetes (most of whom presumably have autoimmune diabetes) a subset of individuals maintains residual beta cell mass despite long term follow-up. The interpretation of this data is complicated by the heterogeneity of Type 1 diabetes with two major pattern of pathology identified in childhood diabetes characterized by the presence or absence of pseudoatrophic islets (i.e. islets without insulin positive cells).

Methods: In order to better assess the prevalence of residual beta cells in patients with autoimmune Type1 diabetes, we utilized samples from the JDRF sponsored nPOD (network of pancreatic organ donors) initiative that were characterized for islet cell autoantibodies as determined by radioimmunoassay for the islet autoantigens GAD65, ICA512 (IA-2) and Znt8. To minimize the possible effect of diabetes heterogeneity in the assessment of beta cell mass preservation in patients with autoimmunity, we defined as “autoimmune diabetes” only clinically defined Type1 diabetes accompanied by positivity for at least one islet autoantibody. When this definition was applied to subjects with long standing diabetes (at least one year of disease duration) screened through the nPOD program, we identified 17 islet antibodies positive donors with mean disease duration of 10.18 years, average age at death of 23.42 years and average age of onset of 13.25 years. In this group, 29% (5/17) of subjects had residual insulin positive cells in the pancreas.

Summary of Results: Quantification of this beta cell mass by morphometric analysis revealed that the mean beta cell mass of subjects whose pancreas contained residual insulin positive beta cells was less than 1% of the mean value in normal controls. These islets show a decreased ratio of beta to non-beta islet cells. This suggests that, albeit not destroyed, they were subject to autoimmune attack. This was also confirmed by the findings of insulinitis in some of these cases. The pancreata of all individuals with Type 1 autoimmune diabetes contained pseudoatrophic islets (regardless of the presence or absence of residual beta cells) (Pattern A beta cell loss).

Conclusions: In conclusion, these data show that autoimmune Type 1 diabetes is characterized by pattern A beta cell loss and a significant proportion of individuals with Type 1 autoimmune diabetes maintains residual beta cells.