Complete Long-Term Recovery of β-Cell Function in Autoimmune Type 1 Diabetes After Insulin Treatment

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Progressive loss of β-cell mass in type 1 diabetes results from $CD4^+$ and $CD8^+$ T-cell autoimmunity targeting insulin and other islet cell antigens. After initial treatment of type 1 diabetes, partial disease remission is found in 18–80% of patients, with a mean duration of only 6–10 months (1).

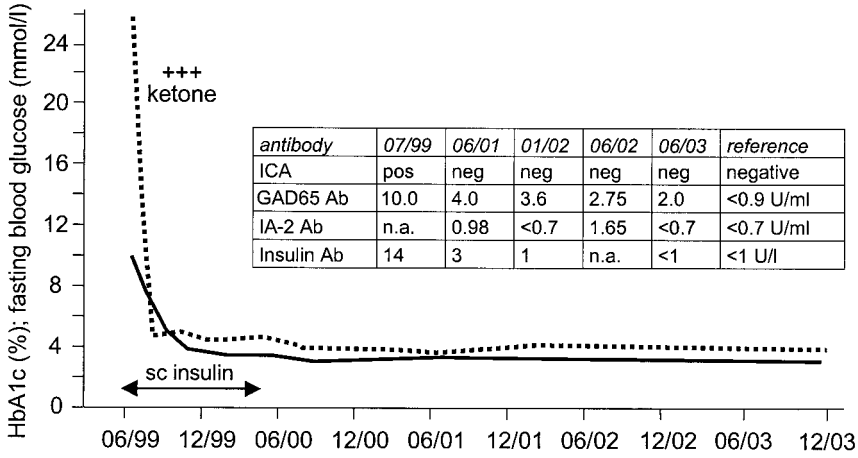
HISTORY AND EXAMINATION

— A 13-year-old Caucasian boy (BMI 26.4 kg/m^2) presented with 3 weeks' history of polyuria, polydipsia, and weight loss. His serum glucose (26.8 mmol/l), HbA_{1c} (9.4%, normal 3.2–5.5) and fructosamine (628 μmol/l, normal 205–285) levels were highly elevated (Fig. 1), and urinalysis showed glucosuria (+++) and ketonuria (+++). He was HLA-DRB1*0101,*0901, DRB4*01, DQA1*0101,03, and DQB1*0303,0501. Plasma C-peptide, determined at a blood glucose of 17.0 mmol/l, was low (0.18 nmol/l). His previous history was unremarkable, and he did not take any medication. The patient received standard treatment with insulin, fluid, and electrolyte replacement and diabetes education. After an uneventful clinical course he was discharged on multiple-injection insulin therapy (total 0.9 units · kg^{-1} · day^{-1}) after 10 days.

Subsequently, insulin doses were gradually reduced to 0.3 units · kg^{-1} · day^{-1}, and insulin treatment was completely stopped after 11 months. Without further treatment, HbA_{1c} and fasting glucose levels remained normal throughout the entire follow-up of currently 4.5 years. During oral glucose tolerance testing performed 48 months after diagnosis, he had normal fasting and 2-h levels of glucose (3.7 and 5.6 mmol/l, respectively), insulin (60.5 and 217.9 pmol/l, respectively), and C-peptide (0.36 and 0.99 nmol/l, respectively). His insulin sensitivity, as determined by insulin sensitivity index (composite) and homeostasis model assessment, was normal, and BMI remained unchanged. Serum autoantibodies to GAD65, insulin autoantibody-2, insulin, and islet cell antibodies were initially positive but showed a progressive decline or loss during follow-up.

INVESTIGATION

— T-cell antigen recognition and cytokine profiles were studied using a library of 21 preproinsulin (PPI) peptides (2). In the patient's peripheral blood mononuclear cells (PBMCs), a high cumulative interleukin (IL)-10 secretion (201 pg/ml) was observed in response to PPI peptides, with predominant recognition of PPI_{44-60} and PPI_{49-65}, while interferon (IFN)-γ secretion was undetectable. In contrast, in PBMCs from a cohort of 12 type 1 diabetic patients without long-term remission (2), there was a dominant IFN-γ response but low IL-10 secretion to PPI. Analysis of $CD4^+$ T–helper cell subsets revealed that IL-10 secretion was mostly attributable to the patient's naïve/recently activated $CD45RA^+$ cells, while a strong IFN-γ response was observed in $CD45RA^-$ cells. $CD45RA^+$ T-cells have been associated with regulatory T-cell function in diabetes, potentially capable of suppressing autoimmune T-cell responsiveness of $CD45RA^-$ T-cells (3). Similarly, $IL\text{-}10^{hi}$ $CD4^+$ T-cells have been described to inhibit experimental autoimmunity (4). It is therefore conceivable that pathogenic immune responsiveness to PPI in this patient



antibody	07/99	06/01	01/02	06/02	06/03	reference
ICA	pos	neg	neg	neg	neg	negative
GAD65 Ab	10.0	4.0	3.6	2.75	2.0	<0.9 U/ml
IA-2 Ab	n.a.	0.98	<0.7	1.65	<0.7	<0.7 U/ml
Insulin Ab	14	3	1	n.a.	<1	<1 U/l

Figure 1—*HbA_{1c} (solid line; reference range 3.2–5.5%), fasting plasma glucose (dotted line), and autoantibody levels* (table insert) *at type 1 diabetes onset (7/99) and during 4.5 years of follow-up.*

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Abbreviations: IFN, interferon; IL, interleukin; PBMC, peripheral blood mononuclear cell; PPI, preproinsulin.

was downregulated by $CD45RA^+$ $IL\text{-}10^{hi}$ T-cell subsets.

CONCLUSIONS — Preservation of β-cell mass is considered the ultimate goal in type 1 diabetes intervention. Our observations show that recovery of β-cell function may occur even after the clinical onset of type 1 diabetes, potentially involving IL-10–dependent regulatory T-cell pathways.

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