

# Complete Long-Term Recovery of $\beta$ -Cell Function in Autoimmune Type 1 Diabetes After Insulin Treatment

BEATE KARGES, MD<sup>1</sup>  
IVANA DURINOVIC-BELLÓ, PHD<sup>2</sup>  
EBERHARD HEINZE, MD<sup>1</sup>

BERNHARD O. BOEHM, MD<sup>2</sup>  
KLAUS-MICHAEL DEBATIN, MD<sup>1</sup>  
WOLFRAM KARGES, MD<sup>2</sup>

**P**rogressive loss of  $\beta$ -cell mass in type 1 diabetes results from CD4<sup>+</sup> and CD8<sup>+</sup> 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).

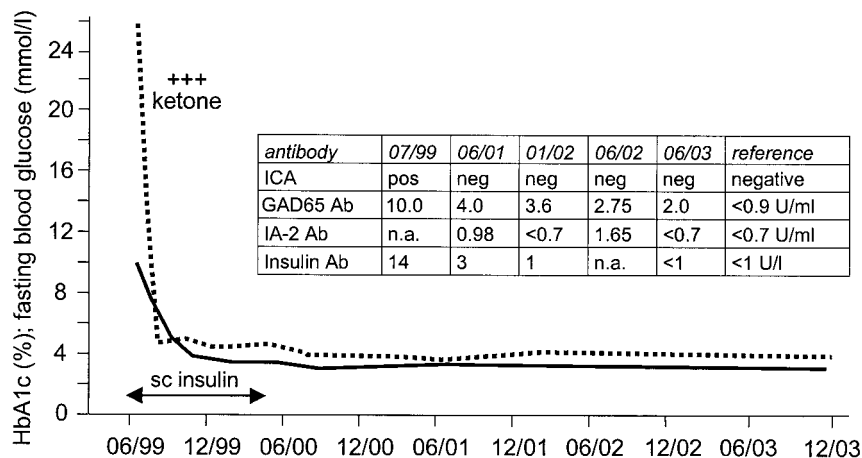
## HISTORY AND EXAMINATION

A 13-year-old Caucasian boy (BMI 26.4 kg/m<sup>2</sup>) presented with 3 weeks' history of polyuria, polydipsia, and weight loss. His serum glucose (26.8 mmol/l), HbA<sub>1c</sub> (9.4%, normal 3.2–5.5) and fructosamine (628  $\mu$ mol/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  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup>) after 10 days.

Subsequently, insulin doses were gradually reduced to 0.3 units  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup>, and insulin treatment was completely stopped after 11 months. Without further treatment, HbA<sub>1c</sub> and fasting glu-

cose 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<sub>44–60</sub> and PPI<sub>49–65</sub>, while interferon (IFN)- $\gamma$  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- $\gamma$  response but low IL-10 secretion to PPI. Analysis of CD4<sup>+</sup> T-helper cell subsets revealed that IL-10 secretion was mostly attributable to the patient's naïve/recently activated CD45RA<sup>+</sup> cells, while a strong IFN- $\gamma$  response was observed in CD45RA<sup>-</sup> cells. CD45RA<sup>+</sup> T-cells have been associated with regulatory T-cell function in diabetes, potentially capable of suppressing



**Figure 1**—HbA<sub>1c</sub> (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.

From the <sup>1</sup>University Children's Hospital, University of Ulm, Ulm, Germany; and the <sup>2</sup>Department of Internal Medicine 1, University of Ulm, Ulm, Germany.

Address correspondence to Dr. Wolfram Karges, MD, Department of Internal Medicine 1, University of Ulm, Robert Koch Strasse 8, 89081 Ulm, Germany. E-mail: wolfram.karges@medizin.uni-ulm.de.

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

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autoimmune T-cell responsiveness of CD45RA<sup>-</sup> T-cells (3). Similarly, IL-10<sup>hi</sup> CD4<sup>+</sup> T-cells have been described to inhibit experimental autoimmunity (4). It is therefore conceivable that pathogenic immune responsiveness to PPI in this patient

was downregulated by CD45RA<sup>+</sup> IL-10<sup>hi</sup> T-cell subsets.

**CONCLUSIONS**— Preservation of  $\beta$ -cell mass is considered the ultimate goal in type 1 diabetes intervention. Our observations show that recovery of  $\beta$ -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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