progression in this and other glomerular diseases [3]. In these patients, however, GFR was still normal at follow-up and the fraction of sclerotic glomeruli only increased from 4% to 8%.

We did study these patients on a regular basis, but only reported and analyzed their data from the two time points corresponding to their renal biopsies. We did not determine quantitative albuminuria during the GFR clearances because of the significant potential for variability associated with bladder emptying in each of the 20-min collection periods. What impact did ACE inhibitors have on our patients? This is difficult to say, as patients often start ACE inhibitors when they deteriorate clinically. For example, the patient with the largest decrease in GFR and the second largest increase in albumin creatinine ratio was on an ACE inhibitor.

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Kevin V. Lemley
Stanford, CA, USA

Absence of protective effect of oral insulin on residual β-cell function in type 1 diabetes

Original article:
Oral insulin administration and residual β-cell function in recent-onset type 1 diabetes: a multicentre randomised controlled trial. Chaillous L, Lefèvre H, Thivolet C et al. *Lancet* 2000; 356: 545–9.

Summary

On the basis that oral administration of insulin prevents autoimmune β-cell destruction in non-obese diabetic (NOD) mice, the authors evaluated the potential protection of oral insulin on residual β-cell function in 131 autoantibody-positive diabetic patients (age range 7–40 years) within 2 weeks of diagnosis.

Three groups of patients were randomly assigned 2.5 mg or 7.5 mg oral insulin daily, or placebo, for 1 year, in addition to subcutaneous optimized insulin therapy. Residual β-cell function was measured by serum C-peptide concentrations in the fasting state and after glucagon or meal stimulation. The putative tolerizing properties of oral insulin were indirectly evaluated by assays of autoantibodies to β-cell antigens (islet cell, insulin, 65 kD isoform of glutamic acid

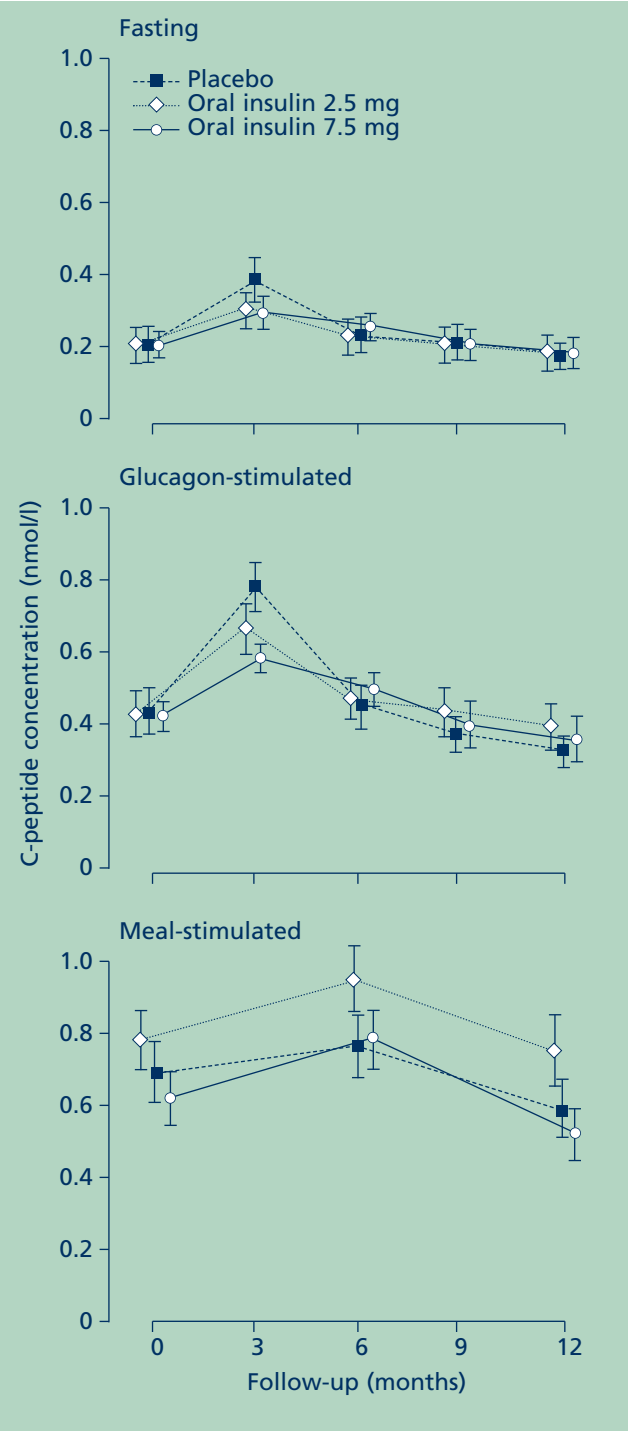

Fig. 1: *Mean fasting, glucagon-stimulated and meal-stimulated C-peptide concentrations in treated type 1 diabetic patients receiving placebo, 2.5 mg or 7.5 mg oral insulin. Error bars show SE.*

decarboxylase [GAD_{65}] and tyrosine phosphatase/islet antigen 2 [IA-2] antibodies).

Baseline C-peptide and HbA_{1c} concentrations were similar in the three groups. During follow-up and after 1 year, the three groups did not significantly differ in subcutaneous insulin requirements, in HbA_{1c} concentrations, or in fasting, glucagon- and meal-stimulated C-peptide concentrations (*Fig. 1*). Neither age nor C-peptide concentration at entry influenced treatment effects. No significant differences appeared in the time-course of antibodies to insulin, GAD_{65} or IA-2.

The authors conclude that, at the doses used in this trial, oral insulin initiated at clinical onset of type 1 diabetes did not prevent or slow the progression of autoimmune β-cell destruction.

Comment

Because oral tolerance closely depends on the dose of antigen administered, it is interesting to note that another study has evaluated the effect of 5 mg oral insulin on residual β-cell function in early-onset type 1 diabetes [1]. Pozzilli et al. also failed to evidence any protective effect of oral insulin in 80 diabetic patients treated by intensive subcutaneous insulin therapy. Moreover, in patients younger than 15 years, a tendency for lower C-peptide concentrations was identified at 9 and 12 months after initiation of oral insulin administration. While the results of the Diabetes Prevention Trial of Type 1 Diabetes (DPT-1) are expected with hope and some anxiety, these two well-conducted independent studies raise some significant doubt about the preventive efficacy of this large multinational trial in subjects at risk for developing type 1 diabetes.

Oral tolerance has been shown to work in some animal models of human autoimmune diseases [2]; recent studies have deciphered a number of cellular and molecular mechanisms underlying mucosal tolerance in such models. Those mechanisms include clonal deletion and anergy of autoreactive T cells with large doses of autoantigen, whereas immunosuppressive transforming growth factor-β-related peptides and active cellular suppression by regulatory T cells can be induced by low doses. In NOD mice, 1 mg of oral porcine insulin given twice weekly is able to prevent autoimmune diabetes and to induce tolerance, but smaller doses do not function [3]. However, a protocol effective in one animal model may be ineffective in another. This is illustrated by the fact that oral insulin does not prevent, and even exacerbates, the diabetogenic autoimmune process in bio-breeding (BB) rats [4]. As recently recalled, one cannot ignore that administration of autoantigen is able to prime and trigger autoimmunity rather than induce immunological tolerance [5].

Immunogenic autoantigens vs. tolerogenic self-antigens

Despite those negative observations, (re)programming of the immunological self-tolerance of islet β-cells continues to be a very rational approach in the prevention of type 1 diabetes. The design of the most appropriate strategy demands a precise knowledge of the mechanisms by which self-tolerance of the β-cell is established in reality. The *thymus* plays a pivotal role in T cell self-tolerance of neuroendocrine principles [6]. Central T cell self-tolerance of the insulin family may follow the expression of insulin-related genes by distinct cell populations following a clear hierarchical pattern in their relative dominance: insulin-like growth factor-2 (*IGF2*) by thymic epithelium > insulin-like growth factor-1 (*IGF1*) by thymic macrophages >> insulin (*INS*) by thymic dendritic cells [7–11]. Other genes coding for β-cell antigens are also expressed within the thymus cellular network [12]. For T cells having escaped the powerful thymic censorship, peripheral tolerogenic mechanisms provide additional brakes for preventing the risk of further autoimmune responses directed to insulin-secreting β-cells. More and more studies are documenting the failure of thymic tolerogenic function in the pathophysiology of autoimmunity. Recently, we reported that the ontogenetic development of β-cell autoimmunity in diabetes-prone BB (BBDP) rats might be associated with a thymus-specific defect of *Igf2* expression [12]. This tissue-specific *Igf2* defect may contribute, together with other genetic mechanisms, both to lymphopenia and absence of central self-tolerance of the insulin hormone family in BBDP rats [13, 14]. The molecular mechanism responsible for the defect of *Igf2* expression in the thymus of these animals remains to be identified. However, since insulin is a specific immunogenic β-cell *autoantigen* and is ineffective in protecting residual β-cell function, the tolerogenic properties of IGF-II (or IGF-II-derived peptides), such as the *self-antigen* of the insulin family, should now be explored as another potential means of preventing type 1 diabetes.

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Summary and Comment:
Vincent Geenen, Liège, Belgium

Persisting islet cell antigens in type 1 diabetes

Original article:
High frequency of persisting or increasing islet-specific autoantibody levels after diagnosis of type 1 diabetes presenting before 40 years of age. Decochez K, Tits J, Coolens J-L et al. *Diabetes Care* 2000; 23: 838–44.

Summary

The authors investigated the presence of major autoantibodies in 194 type 1 diabetic patients below 40 years of age, including antibodies to islet cell (ICA), glutamic acid decarboxylase 65 (GADA) and tyrosine phosphatase (IA-2A), at diagnosis and during 4 years of follow-up.

The percentage of patients positive for at least one antibody remained very high 4 years after diagnosis (*Table I*), suggesting the persistence of islet cell antigens. Two of the 14 initially antibody-negative patients became antibody-positive after diagnosis. The divergent temporal patterns of appearance of ICA, GADA and IA-2A suggest that the ICA test reflects the presence of other autoimmune processes. Finally, the number of patients with autoimmune type 1 diabetes may be underestimated if assays with low sensitivity are used. GADA assays have the best diagnostic sensitivity after clinical onset of the disease.

Comment

Measurement of different autoantibodies to islet cell antigens in patients with type 1 diabetes at diagnosis is not currently used as a parameter for diagnosis. Its use is based mainly on clinical grounds and ICA are measured only when the diagnosis of diabetes type is uncertain.

In research settings ICA, GADA or IA-2A are useful parameters for assessing the extent of β-cell autoimmunity and for correlation analysis with other data. This *modus operandi* should clearly be extended to clinical settings too. The paper by Decochez et al. clearly showed the persistence of islet cell antigen-related antibodies in type 1 diabetic patients after diagnosis. This finding suggests the presence of β-cell antigens as well as β-cell function, as testified by residual C-peptide secretion several years after diagnosis.

Intervention at diagnosis with intensive insulin therapy and possible adjuvant therapy such as nicotinamide is aimed not only at controlling