OBSERVATIONS

Does Therapy With Anti–TNF-α Improve Glucose Tolerance and Control in Patients With Type 2 Diabetes?

Type 2 diabetes is associated with insulin resistance (IR). IR is partially caused by the cytokine tumor necrosis factor-α (TNF-α), which is produced in inflammatory fat tissue in muscle, liver, and adipose tissue. Inflamed abdominal fat releases adipokines and inflammatory cytokines, one of which is TNF-α. Past experimental studies using anti–TNF-α therapy in type 2 diabetic patients have been limited in both time and dosage because of the toxicity of these agents.

We designed a retrospective study in which anti–TNF-α agents were used in larger therapeutic doses for up to 10 years in patients with rheumatoid arthritis (RA) and Crohn's disease (CR). We assessed the effects of this treatment on control of type 2 diabetes. Eight Veterans Affairs patients with RA or CR and type 2 diabetes and a matched group of control patients with both diagnoses were studied over 10 years by chart review before and after anti–TNF-α therapy. In order to assess the effect of anti–TNF-α prescription on glucose tolerance, we averaged blood glucose for each treatment patient before and during the last year of treatment. The anti–TNF-α medications used were entanercept by injection of 50 mg each week and infliximab as a large intravenous bolus every 6–8 weeks.

We assessed control of diabetes using fasting blood glucose (FBG), HbA_{1c}, and fasting plasma triglyceride (TG) values. Eight patients had an average FBG of 142 mg/dL before treatment; after initiation of treatment, the average FBG was 126 mg/dL, $P < 0.01$; and in the last full year of treatment, FBG was 121 mg/dL, $P < 0.01$. In select cases, average HbA_{1c} was 6.5% before and 5.5% after treatment, and TGs were 350 mg/dL before versus 200 mg/dL after therapy, and unchanged in control subjects with CR. Thus, patients with RA or CR and type 2 diabetes, who were also receiving anti–TNF-α treatment for their autoimmune disease, had significant improvement in their FBG, HbA_{1c}, and TG values. Knowing that TNF-α is produced by oxidative stress in fat imbedded in skeletal muscle and liver, these results make a powerful case for endogenous TNF-α being a causative factor in the IR of type 2 diabetes.

Many studies have demonstrated the ability of TNF-α to induce IR (1,2). The most successful of these have been in vitro or small animal experiments, including many from our own laboratories (1,2). Dose of anti–TNF-α therapy and duration of treatment has been minimal in most of these studies because of the toxicity of the drugs (3). Despite the limitations caused by a retrospective study and lack of closer monitoring of patients' diabetes, our data has value. It not only shows before and after with highly matched control subjects, but also examines higher doses of anti–TNF-α agents and longer duration of treatment. This provides an experimental design that is able to identify a role of TNF-α as a major effecter of IR in humans with type 2 diabetes. It is clear that more studies will be needed, particularly prospective studies, to solidify our results.

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