CASE REPORT

Decrease of fructosamine levels during treatment with adalimumab in patients with both diabetes and rheumatoid arthritis

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Abstract

Tumour necrosis factor α (TNF α) is a pro-inflammatory cytokine which has been closely linked to obesity and insulin resistance. We present two cases of patients with rheumatoid arthritis (RA) and concomitant diabetes mellitus, who showed a marked decrease of fructosamine levels after initiating therapy with adalimumab, a TNF α -blocking agent, for active RA. This finding may implicate that TNF α blockade causes better glycaemic control in RA patients with concomitant diabetes, possibly by improving insulin resistance.

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Introduction

Tumour necrosis factor α (TNF α), a pro-inflammatory cytokine, plays an important role in inflammatory and autoimmune diseases like rheumatoid arthritis (RA). TNF α has also been closely linked to obesity and insulin resistance (1). Increased insulin resistance, just as RA (2), is an important risk factor for developing cardiovascular disease (CVD) (3). Thus far, the role of TNF α in insulin resistance has remained controversial. Despite a clear reversal of insulin resistance by TNF α neutralization in animal models (4, 5), two studies in humans did not show an effect of administration of either a chimeric anti-TNF α antibody (6) or a recombinant soluble TNF α receptor (7) on insulin sensitivity in obese or type 2 diabetes patients. However, recently it was shown that TNF α infusion impairs glucose uptake in human skeletal muscle by altering insulin signal transduction (8) and induces insulin resistance in healthy volunteers (9). Moreover, TNF α antagonists, in addition to their known powerful anti-inflammatory effects, may have a beneficial effect on insulin resistance in rheumatic diseases (10–12). Beneficial clinical effects of treatment of RA with TNF α antagonists on concomitant diabetes have not been described. We describe herein two cases of RA patients with concomitant diabetes in which glycaemic control parameters changed after initiation of adalimumab therapy.

Research design and methods

A patient with known diabetes type 1 and concomitant RA showed a marked improvement of HbA1c levels after initiation of adalimumab, a recombinant human IgG1-MAB, therapy for active RA when she visited the endocrinologist (SS) in the VUmc. Due to this finding, the effect of adalimumab on fructosamine levels was assessed through measuring fasting fructosamine levels over time in RA patients, according to the 1987 American College of Rheumatology criteria, with concomitant diabetes before and during adalimumab therapy. A survey into a cohort of RA patients treated with adalimumab in the Jan van Breemen Institute, a large outpatient clinic for rheumatology, was conducted to identify RA patients with concomitant diabetes, i.e. type 1 and type 2 diabetes according to WHO criteria. Further inclusion criteria were: (a) no concomitant use of prednisone around the start and during the use of adalimumab; (b) ≥ 3 stored, deep-frozen serial serum samples available, of which at least one <1 month before and one during adalimumab therapy and (c) use of a stable adalimumab dose in the period of serum sample collection. On further analysis, five of seven patients initially recruited did not meet these criteria and were excluded: three patients used concomitant prednisone in decreasing dosage, one patient was noncompliant to adalimumab therapy and of one patient no serum sample was available <1 month

before start with adalimumab. Of the remaining two patients, fructosamine levels were determined in all available serum samples. Medical records were used to collect clinical data. Information regarding dietary habits and physical activity patterns was collected by phone.

Fructosamine measurement

As only serum was available fructosamine was chosen as reference for glycaemic control. The serum fructosamine concentration is an indicator of glycosylated serum protein and reflects the average blood glucose level over 1–3 weeks. Therefore, serum fructosamine level is a useful marker to assess short-term glucose control. Serum fructosamine levels were measured in VUmc by means of a validated, commercially available method.

Statistical analysis

To investigate whether fructosamine levels changed significantly before and after adalimumab treatment, the following technique was used. First, the data of both patients were pooled. Subsequently, a regression line was drawn through all fructosamine values collected after the start with adalimumab (same time-points for both patients). This regression line was extended towards the time-point corresponding with the 'pooled' fructosamine level before the start with adalimumab using the most negative regression coefficient possible, i.e. the lower bound of the 95% confidence interval (95% CI) of the regression coefficient. At this point, we calculated the upper bound of the 95% CI. This value was compared with the observed value.

Results

Two RA patients with diabetes were included: one 40-year-old female with type 1 diabetes since 18 years (index patient) and one 66-year-old male with type 2 diabetes since 9 months. These patients showed a substantial decrease in fructosamine levels after the start with adalimumab (Fig. 1). Blood glucose lowering therapy consisted of 50 units of human insulin per day in patient 1 and glimepiride 2 mg per day in patient 2 and remained stable during the treatment period. Dietary and physical habits did not change.

Conclusion

Our results illustrate a fast and substantial decline in fructosamine levels in two patients with RA and concomitant diabetes after initiation of treatment with adalimumab. The improved glycaemic control is

Figure 1 Pooled fructosamine, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in patients 1 and 2 over time (months). The arrow indicates the start with adalimumab.

in accordance with a previous report of a psoriatic arthritis patient in which type 2 diabetes disappeared upon treatment with infliximab, suggesting an improvement of insulin sensitivity (12). However, in this case report, the improvement of glycaemic control occurred after prolonged treatment (4–5 months) with infliximab, while we found a faster response. Type 2 diabetes is characterized by insulin resistance of the major target tissues and (relative) β -cell failure, leading to decreased insulin secretion. In general, $\text{TNF}\alpha$ plays a role in the pathophysiology of diabetes. $\text{TNF}\alpha$ is synthesized and secreted by adipose tissue and regulates insulin receptor function by impairing insulin signalling (13). Moreover, $\text{TNF}\alpha$ plasma levels are increased in type 1 diabetes and are associated with long-term glycaemic control parameters, among them HbA1c and fructosamine (14). Furthermore, it is clear that RA patients have enhanced serum levels of $\text{TNF}\alpha$ due to the presence of chronic systemic inflammation. Hence, we hypothesize that $\text{TNF}\alpha$ blockade has improved insulin signalling in both patients, subsequently leading to a decrease of fructosamine levels and thereby better glycaemic control. This theory is supported by the fact that: (1) the administered glucose lowering therapy remained stable and dietary and physical activity patterns did not change around the start of adalimumab therapy, and (2) inflammatory markers were not substantially elevated before treatment, implicating that their contribution to the decline of fructosamine levels is probably small. However, we cannot exclude the possibility that this improved glycaemic control is partly due to alterations in inflammatory activity. Our findings indicate that $\text{TNF}\alpha$ blockade causes better glycaemic control in RA patients with concomitant diabetes by improving insulin resistance, which may explain why $\text{TNF}\alpha$ antagonists decrease the risk of first incidence of CVD in RA (15). Moreover, clinically, physicians should be aware of the possibility influencing diabetes by

aggressive treatment of RA with TNF α antagonists. Further prospective research is required.

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