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Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis

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Abstract
Objective: Tumor necrosis factor alpha (TNF-alpha) might be an important mediator of insulin resistance. Infliximab is a chimeric monoclonal, high-affinity antibody against the soluble and trans-membrane TNF-alpha. It can reduce significantly the biological activity of circulating and tissue TNF-alpha and is used in the treatment of various autoimmune disorders. The purpose of the study was to assess the effects of infliximab infusions on insulin sensitivity in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

Methods: Forty-five patients (28 with RA and 17 with AS) aged 19 to 74 years were studied. All patients were treated with intravenous infliximab. A complete biochemical profile was performed before and after 6 months of treatment with infliximab. As a measure of insulin sensitivity the Homeostasis Model Assessment (HOMA) index was used and as a measure of insulin sensitivity the Quantitative Insulin Sensitivity Check Index (QUICKI) index was used.

Results: In the whole study population group, no significant changes of HOMA index or of QUICKI index were observed. However, in the tertile of patients with the highest insulin resistance, a significant decrease of HOMA index and increase of QUICKI index was found (p<0.01 for both parameters).

Conclusions: The results of the present study may indicate that infliximab treatment might have beneficial effects on insulin sensitivity in the most insulin resistant patients with RA and AS.

Key words: Insulin resistance, Infliximab, Rheumatoid arthritis, Ankylosing spondylitis, Tumor necrosis factor alpha
It is well established that there is increased risk for cardiovascular disease (CVD) in rheumatoid arthritis (RA) [1, 2]. Several factors have been implicated for it. Systemic inflammation is considered the major one.

Increased insulin resistance is an important risk factor for CVD [3]. Patients with autoimmune connective tissue diseases have increased insulin resistance [4]. Several factors have been implicated in the pathogenesis of insulin resistance. Tumor necrosis factor alpha (TNF-alpha) is a proinflammatory cytokine that plays a major role in the pathogenesis of autoimmune diseases and inflammatory disorders. Recently, many studies suggested that TNF-alpha might be an important mediator of insulin resistance in animal models [5, 6]. Moreover, there is evidence that in insulin resistant patients TNF-alpha overexpression occurs in adipose tissue and skeletal muscle [7, 8]. Weight loss in obese insulin resistant subjects results in a substantial reduction of TNF-alpha expression and secretion, in association with a decrease in serum TNF-alpha levels and a restoration of insulin sensitivity [9]. Interestingly, administration of TNF-alpha to healthy volunteers induced insulin resistance [10]. Infliximab is a chimeric monoclonal, high-affinity antibody against the soluble and trans-membrane TNF-alpha. It can reduce significantly the biological activity of circulating and tissue TNF-alpha and is used in the treatment of various autoimmune disorders.

Very few data exist about the role of infliximab treatment on insulin sensitivity [11]. Thus, we assessed the effects of infliximab infusions on insulin sensitivity in patients with RA and ankylosing spondylitis (AS).

MATERIALS AND METHODS
Forty-five patients (28 with RA and 17 with AS) aged 19 to 74 years were studied. The patients with RA who were refractory or did not tolerate two disease modifying antirheumatic drugs (DMARDs), were treated with intravenous infliximab (3 mg/kg/weight) at 0, 2, 6, and every 8 weeks thereafter for a total period of 12 months. Rheumatoid patients also received prednisone (5 mg/day) and cyclosporin A or methotrexate. The dose of the drugs was stable during the study.

All patients with AS had axial disease, receiving only non-steroids anti-inflammatory drugs, were treated with infliximab (5 mg/kg/weight) with the same protocol as above.

Patients were excluded from the study if they had: (i) a history or presence of malignant disease, (ii) known liver or kidney abnormalities or history or viral hepatitis B and C, (iii) major complicating diseases such as amyloidosis or heart or lung disease, (iv) diabetes mellitus, (v) endocrine or metabolic disorders, (vi) drugs which may influence glucose metabolism, and (vii) a positive tuberculin skin test or abnormal chest x-ray.

All participants reported no significant change in their body weight for at least 3 months prior to entry into the study. Apart from clinical assessment a complete biochemical profile was performed before and after 6 months of treatment with infliximab. As a measure of insulin resistance the Homeostasis Model Assessment (HOMA) index was used and as a measure of insulin sensitivity the Quantitative Insulin Sensitivity Check Index (QUICKI) index was used.

Statistical analysis was performed with the non-parametric Wilcoxon test and the Spearman correlation coefficients.

RESULTS
The clinical response of RA and AS patients has been reported previously [11, 12]. Body mass index and waist to hip ratio did not change significantly after 6 months of treatment. In the whole study, no significant changes of HOMA index or of QUICKI index were observed in the population group. However, in the tertile of patients with the highest insulin resistance,
a significant decrease of HOMA index and increase of QUICKI index was found (p<0.01 for both parameters) (table 1). No significant differences were observed regarding the two insulin action indexes between the patients with RA and AS. Moreover, no significant correlations were observed between the insulin action indexes and age, disease duration or with disease activity.

**Table 1** Effects of infliximab treatment on insulin resistance in the tertile of patients with the highest insulin resistance (n=14)

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-R</td>
<td>3.01±0.48</td>
<td>1.89±0.35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.30±0.008</td>
<td>0.35±0.013</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard error

**DISCUSSION**

In the present study a significant decrease in insulin resistance was observed after infliximab treatment in the most insulin resistant patients. It cannot be completely excluded the possibility that other factors might have affected the insulin sensitivity in these patients. However, the lack of change of their body weight and their dietary habits, as well as the fact that the dose of steroids and DMARDs (that both could affect considerably the insulin resistance) [13, 14] indicate that the most probable cause of the improvement in insulin sensitivity was infliximab therapy. Only one small study has previously assessed the effects of infliximab on insulin resistance [15]. The authors did not find a significant change of insulin sensitivity after 3 to 5 infusions of infliximab. However, due to the very small number of patients included (10 subjects) they did not perform a separate analysis of the patients with the highest insulin resistance. In another study, the administration of another human anti-TNF-alpha antibody (CDP 571) did not affect considerably the insulin sensitivity and the glycemic control in patients with type 2 diabetes mellitus [16]. However, those subjects had long-lasting diabetes mellitus (known duration of the disease averaging 9 years) and severe hyperglycemia. In such patients, various other mechanisms may contribute to the insulin resistance, including hyperglycemia, which has been shown to affect insulin signalling in a different way than that of TNF-alpha [17].

In conclusion, our results indicate that infliximab treatment might have beneficial effects on insulin sensitivity in the most insulin resistant patients with RA and AS. The improvement in insulin sensitivity might decrease the CVD risk in these patients. Further prospective studies are needed in large population groups followed for a long period of time in order to assess the effects of infliximab therapy on cardiovascular risk.
REFERENCES


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