Anti-tumor necrosis factor-α blockade improves insulin resistance in patients with rheumatoid arthritis

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ABSTRACT

Objective. *Systemic inflammation, insulin resistance, and endothelial dysfunction have been implicated in the development of cardiovascular disease in rheumatoid arthritis (RA). Since insulin resistance can promote endothelial dysfunction and anti-TNF-α blockade yield a rapid improvement of endothelial function, we have sought to assess whether TNF-α blockade may also result in a reduction of insulin serum levels and improvement of insulin resistance in RA patients who require this therapy because of severe and refractory disease.*

Methods. *We recruited patients with RA seen over a period of 1 month at Hospital Xeral-Calde, Lugo, Spain, that were on treatment with anti-TNF-α monoclonal antibody-infliximab. Patients with diabetes mellitus or plasma glucose > 110 mg/dl were excluded. Fasting blood samples were taken for determination of plasma glucose and serum insulin levels immediately prior to and after infliximab infusion.*

Results. *Twenty-seven RA patients (21 women; mean age: 57.1 years; mean DAS28: 4.43) fulfilled the inclusion criteria. Dramatic reduction in the serum insulin levels and insulin/glucose index was observed following infliximab infusion. Also, a significant improvement of insulin resistance and insulin sensitivity was found.*

Conclusions. *Our study confirms a rapid beneficial effect of infliximab on insulin resistance and insulin sensitivity in RA patients treated periodically with this drug. It may support the long-term use of drugs that act blocking TNF-α function to reduce the mechanisms implicated in the development of atherosclerosis in patients with RA.*

Introduction

Cardiovascular disease is the commonest cause of premature mortality in patients with rheumatoid arthritis (RA) (1). Besides increased mortality due to cardiovascular disease (2), high morbidity due to cardiovascular and cerebrovascular complications is also present in these patients (3). With respect to this, del Rincon *et al.* reported a 3.9-fold increased incidence ratio of cardiovascular events in 236 consecutive patients with RA followed for one year (4).

The increased risk for cardiovascular disease in patients with RA is a consequence of atherosclerosis (5). As reported in Japan and Korea (6, 7), we have recently confirmed the presence of severe subclinical atherosclerotic disease in actively treated Spanish RA patients without clinical evidence of atherosclerosis or cardiovascular risk factors (8).

Insulin resistance and systemic inflammation have been implicated in the development of cardiovascular disease in RA (9, 10). Endothelial dysfunction has been also found in long-term actively treated RA patients without clinically evident cardiovascular disease (11). Since vascular endothelial dysfunction is closely linked to the development of atherosclerosis, this finding may be a critical and early step in the development of atherosclerosis in RA patients.

Several mechanisms that link systemic inflammation may promote the development of endothelial dysfunction in RA (10). Targeted tumor necrosis factor-alpha (TNF-α) antagonists, have had a significant impact on the treatment of patients with RA. In general, the benefit/risk ratio for these agents has been quite favorable (12). In this regard, short-term and long-term TNF-α blockade using the antagonist drug infliximab reduced disease activity and significantly improved endothelial function in RA patients (13, 14). Since insulin resistance can promote endothelial dysfunction, we have sought to assess whether TNF-α blockade may result in a reduction of insulin serum levels and improvement of insulin resistance in RA patients who require this therapy because of severe and refractory disease.

Patients and methods

Patients

Patients who met the 1987 American College of Rheumatology classification criteria for RA (15) and were treated by the same group of rheumatologists (MAG-G, CG-P and AS-A) were recruited from Hospital Xeral-Calde, Lugo, Northwest Spain. The cohort

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constituted a series of patients attending hospital outpatient clinics seen over a period of 1 month (February 2004).

Since the purpose of this study was to assess insulin response following anti-TNF-α therapy in RA patients on periodical treatment with infliximab due to severe and refractory disease, for ethical reasons, patients included in the present study were not randomized to a placebo group. The same procedure has been found acceptable and followed in a recent study on the effect of infliximab therapy on the lipid profile in patients with RA (16).

Patients on treatment with infliximab seen during the period of recruitment with diabetes mellitus or with plasma glucose levels greater than 110 mg/dl (n = 4) were excluded. Also, one patient was excluded because she developed hyperthyroidism. In all cases anti-TNF-α monoclonal antibody-infliximab was prescribed because of the severity of the disease.

In all patients, treatment with a DMARD had been initiated when a diagnosis of RA was made. Prior to anti-TNF-α therapy patients were required to have been treated with at least two disease modifying anti-rheumatic drugs (DMARDs) including chloroquine, sulphasalazine, gold, methotrexate (at least 15 mg/week), leflunomide, and cyclosporine A (3 mg/Kg/day).

Besides non-steroidal anti-inflammatory drugs, all had received treatment with low doses of prednisone (generally 5 mg bid) immediately after disease diagnosis. When this study was performed all patients were on treatment with methotrexate (range 15 to 25 mg/week) with or without chloroquine (250 mg/day) and prednisone (range 2.5 to 7.5 mg/day) plus infliximab 3 or 5 mg/kg/intravenously every 6 or 8 weeks according to disease severity.

The local institutional committee approved anti-TNF-α therapy. Also, patients gave informed consent to participate in this study. Neither this study nor the former one (14) were supported by any pharmaceutical drug company.

Study protocol

In each patient a disease activity score (DAS)28 (17) was assessed prior to infliximab infusion. In all cases the drug was given at 8 a.m. as intravenous infusion in saline solution over 120 minutes. None of the patients did receive any nutrient before and during infusion.

Fasting blood samples were taken for determination of plasma glucose and serum insulin (μU/ml) levels. They were determined immediately prior to the onset of infliximab infusion (time 0) and just at the end of infliximab infusion (time 120). Serum insulin was assessed by the commercial kit DPC (Dipesa, Los Angeles, CA, USA).

While the hyperinsulinemic euglycemic clamp technique is the gold standard, the QUICKI and HOMA are surrogate markers of insulin resistance that are widely used. Due to this, insulin resistance was estimated immediately before and after infliximab infusion by the homeostasis model assessment for insulin resistance (HOMA) using the following formula = serum insulin (μU/ml) x plasma glucose (mmol/l)/22.5 (18), and the quantitative insulin sensitivity check index (QUICKI) using the formula = 1/log insulin (μU/ml) + log glucose (mg/dl) (19). Although results on insulin/glucose index, HOMA and QUICKI are shown in this report; the use of the QUICKI is superior to the HOMA and insulin/glucose index since the variables are logarithmically transformed (19).

Statistical analyses

Insulin and glucose levels and insulin/glucose index, HOMA and QUICKI before (time 0) and post-infusion (time 120) were compared using the paired Student t-test. Comparisons were adjusted by age, sex, DAS28, and body mass index (BMI) (calculated as weight in kilograms divided by height in squared meters). Statistical significance was accepted at $p \leq 0.05$.

Results

Twenty-seven patients fulfilled the inclusion criteria. The main features of the patients are summarized in Table I. At the time of the study 22 of the 27 RA patients still had active disease

Table I. Description of 27 patients on treatment with anti-TNF-α (infliximab) because of RA refractory to at least two DMARDs.

Variable	Mean ± SD or no. (%)
Women	21 (77.8%)
Age (years)	
median (range)	57.1 ± 12.6
	60 (24 –74)
BMI (kg/m²)	
median (range)	25.4 ± 3.9
	24.1 (19.5 – 33.1)
BMI < 25	14 (51.9%)
BMI 25-30	9 (33.3%)
BMI > 30	4 (14.8%)
DAS28	4.43 ± 1.12
median (range)	4.39 (2.58 – 7.02)
Infliximab dose:	
3 mg / 8 weeks	15 (55.6%)
5 mg / 6 weeks	8 (29.6%)
5 mg / 8 weeks	4 (14.8%)

(DAS28 greater than 3.2) (17). Five patients who had previously been switched from standard therapy to infliximab because of severe and active disease had at the time of this study a DAS28 less than 3.2. In all of them plasma glucose level assessed immediately before and after infliximab infusion was less than 110 mg/dl.

As shown in Table II, a dramatic reduction in the serum insulin levels following infliximab infusion was found. As a consequence, a statistically significant reduction in the insulin/glucose index was observed. Also, a significant improvement of insulin resistance and insulin sensitivity was found (Table II). Insulin/glucose index was determined in each of the 27 RA patients before (time 0) and after infliximab infusion (time 120). In two patients insulin/glucose index did not change and in another it increased. In the remaining 24 patients a reduction in the insulin/glucose index following the infusion of the drug was observed.

Also, insulin resistance (HOMA) and insulin sensitivity (QUICKI) (Fig. 1) improved dramatically in most patients following anti-TNF-α therapy.

A low QUICKI is known to be in keeping with insulin resistance. Apart from disease activity, obesity was shown to contribute to insulin resistance in inflammatory arthritis (20). This may explain why post-infusion QUICKI was

Table II. Differences between basal (time 0) and post-infusion (time 120 minutes) glucose and insulin levels, insulin/glucose index, HOMA, and QUICKI.

	Basal (time 0) Mean ± SD	Post-infusion (time120) Mean ± SD	p
Plasma glucose (mg/dl)	84.3 ± 12.0	92.0 ± 8.0	0.0007
Serum insulin (μU/ml)	15.9 ± 10.1	11.5 ± 8.6	0.0001
Insulin/glucose index	0.188 ± 0.114	0.121 ± 0.087	< 0.0001
HOMA	3.4 ± 2.3	2.7 ± 2.2	0.009
QUICKI	0.331 ± 0.031	0.344 ± 0.035	0.004
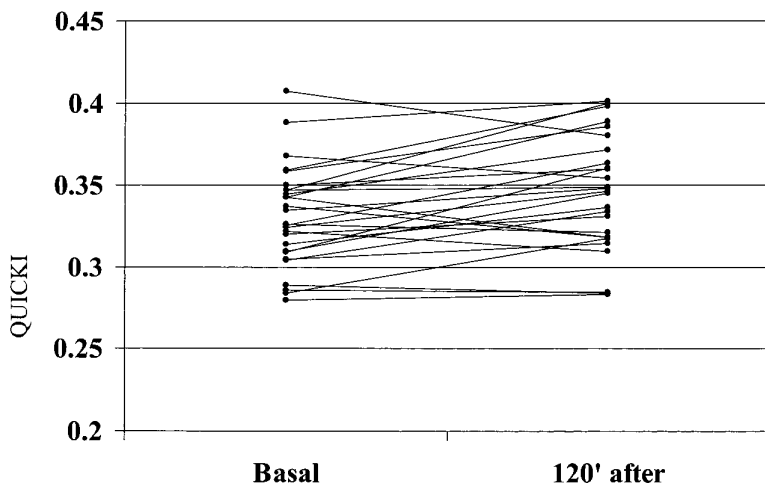
Fig. 1. Improvement of insulin sensitivity (QUICKI) in most patients following anti-TNF-α therapy.

associated with BMI and not with other outcome variables assessed (age, sex, DAS28, infliximab dosage or interval between doses) in our study (data not shown). In this regard, in this series of RA patients with refractory disease to standard therapy a high BMI was predictive of less improvement in insulin sensitivity following infliximab infusion.

Discussion

Chimeric monoclonal anti-TNF-α antibody-infliximab alone or in combination with low-dose MTX is an effective therapy in RA (12, 21). The present study shows that patients with severe RA on treatment with infliximab, which specifically and with high affinity binds to TNF-α and neutralizes this cytokine, also experience a rapid and dramatic reduction in the serum insulin levels and insulin/glucose index. Also, following this therapy a rapid improvement of insulin resistance and insulin sensitivity was observed. Interestingly, in a recent study, Kiortsis *et al*. performed a complete biochemical profile before and after 6 month's treatment with infliximab in 17 patients with ankylosing spondylitis and 28 with RA (22). These authors found a significant decrease of the HOMA index and increase of the QUICKI in the tertile of their patients with the highest insulin resistance (22).

Anti-TNF-α monoclonal antibody-infliximab blocks inflammation by inhibiting the downstream effects of this cytokine (13). More than two decades ago Scandinavian investigators described the presence of glucose intolerance in patients with RA and other chronic inflammatory diseases (23). The degree of the impaired glucose handling was related to the severity of inflammatory activity as defined by acute phase reactants (23). The same group of investigators found that in patients with active RA the impaired glucose handling combined with hyperinsulinemia was directly related to peripheral insulin resistance (24). They observed that peripheral insulin sensiti-

vity was closely associated with the intensity of the inflammatory reaction (24). Of note, although corticosteroids are known to be diabetogenic by increasing the peripheral insulin resistance, prednisolone therapy was found to improve the peripheral insulin sensitivity in patients with RA due to the anti-inflammatory effect of this drug (23, 24). More recently, Paolisso *et al*. confirmed the presence of insulin resistance in different chronic inflammatory diseases and found that insulin resistance is mainly confined to muscular, rather than hepatic site (25). Dessein *et al*. reported that the acute phase response predicts insulin resistance in RA (26). Insulin resistance is also associated with decreased stress responsiveness of the hypothalamic-pituitary-adrenal-axis (27, 28), and endothelial dysfunction (29).

TNF-α production is increased under chronic hyperglycemia and TNF-α has harmful effects on insulin sensitivity and possibly on chronic diabetic complications (30). TNF-α is an important mediator of insulin resistance in obesity and diabetes through its ability to decrease the tyrosine kinase activity of the insulin receptor (31). TNF-α directly impedes insulin-glucose mediated uptake in the skeletal muscle (31).

Together with previous reports, our observations may suggest that anti-TNF-α blockade has concurrent beneficial effects on disease activity (13), endothelial dysfunction (13, 14), and insulin resistance. This may support the long-term use of drugs that act by blocking TNF-α and thereby reduce the mechanisms implicated in the development of atherosclerosis in patients with RA.

However, as observed on endothelial function (14), the rapid beneficial effect of infliximab on insulin resistance may also be transient. If this proves to be the case, the search for TNF-α antagonists with long lasting effects on disease activity, endothelial function and insulin resistance may be needed to decrease the high incidence of cardiovascular complications associated with RA.

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don, nurse from the Rheumatology outpatient Clinic, and the members of the Biochemistry Department from Hospital Xeral-Calde for their valuable help to undertake this study.

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