TNF-alpha antagonist therapy improves insulin sensitivity in non-diabetic ankylosing spondylitis patients

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Abstract

Objectives

Since insulin resistance can promote endothelial dysfunction, and anti-TNF-α treatment improves endothelial function in ankylosing spondylitis (AS) patients, in the present study we sought to assess whether an infusion of the anti-TNF-α monoclonal antibody-infliximab may improve insulin sensitivity in non-diabetic AS patients.

Methods

We assessed a series of 30 non-diabetic patients with AS attending hospital outpatient clinics who fulfilled the modified New York diagnostic criteria for AS. In all cases, the drug was given as an intravenous infusion in a saline solution over 120 minutes. Fasting blood samples were taken for determination of plasma glucose and serum insulin levels immediately before (time 0) and after infliximab infusion (time 120).

Results

At the time of the study only 8 (26.7%) of the 30 patients fulfilled definitions for insulin resistance as HOMA index was in most cases less than 2.29. Nevertheless, a statistically significant reduction in the HOMA values was observed when results found at time 0 (mean±SD: 1.72±1.22) were compared with those observed immediately after infliximab infusion (1.18±0.94) ($p<0.001$). The reduction in HOMA values was more important in those patients with the higher values of HOMA before infliximab infusion. Also, a significant improvement of insulin sensitivity was observed in most patients when QUICKI values before (0.37±0.04) and after infusion (0.39±0.04) were compared ($p=0.004$).

Conclusion

The present study shows that non-diabetic patients with AS on treatment with infliximab experience a rapid improvement of insulin sensitivity following administration of this drug.

Key words

ankylosing spondylitis, atherosclerosis, inflammation, anti-TNF-α antibody-infliximab, insulin resistance, insulin sensitivity

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Introduction

Ankylosing spondylitis (AS), the prototype of spondyloarthropathy, has been associated with a 1.5–2.0 increased mortality rate compared to that in the general population, which is largely due to cardiovascular (CV) complications (1). In this regard, the prevalence rate for myocardial infarction in Dutch individuals with AS was found to be increased approximately 2- to 3-fold compared to the rate in the general population.

Accelerated atherosclerotic disease seems to play the major role in the increased mortality observed in AS (2). Several investigators found increased common carotid artery intima-media wall thickness in patients with AS compared to controls, indicating early subclinical atherosclerosis associated with AS (3-5).

Insulin resistance and systemic inflammation have been implicated in the development of CV disease in rheumatoid arthritis (RA), the prototype of chronic inflammatory disease leading to accelerated atherogenesis (6-8). As previously observed in RA (9), recent studies have also disclosed impaired endothelial function in patients with AS (5, 10, 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 both RA and AS patients.

Several mechanisms that link systemic inflammation have been postulated to promote the development of endothelial dysfunction in RA (7). It is plausible to think that the same mechanisms may also be implicated in the development of accelerated atherogenesis in AS. As observed in RA, targeted tumour necrosis factor-alpha (TNF-α) antagonists, have yielded significant impact on the treatment of patients with spondolarthropathies and specifically in AS (12,-14). Interestingly, Kiortsis *et al*. performed a complete biochemical profile before and after 6 month's treatment with infliximab in 17 patients with AS (15). 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 (15). Since insulin resistance can promote endothelial dysfunction, and anti-TNF-α treatment has been found to improve endothelial function in AS patients (11), in the present study we sought to assess whether an infusion of the anti-TNF-α monoclonal antibody-infliximab may improve insulin sensitivity in non-diabetic AS patients who required this therapy because of disease refractory to non-steroidal anti-inflammatory drugs (NSAIDs).

Patients and methods

Patients

We assessed a series of 30 patients with AS attending hospital outpatient clinics seen over 14 months (January 2009 to March 2010), who fulfilled the modified New York diagnostic criteria for AS (16). They were treated by the same group of rheumatologists and were recruited from the Hospital Xeral-Calde, Lugo, Spain.

Since the purpose of this study was to assess short-term insulin response following anti-TNF-α therapy in AS patients on periodical treatment with infliximab, for ethical reasons, patients included in the present study were not randomised to a placebo group. The same procedure has been found acceptable and followed in studies on the short-term effect of infliximab therapy on the lipid profile in patients with RA (17).

Patients on treatment with infliximab seen during the period of recruitment with diabetes mellitus or with plasma glucose levels greater than 110 mg/dl were excluded. None of the patients included in the study had hyperthyroidism or renal insufficiency. Also, patients seen during the recruitment period who had experienced CV events, including ischaemic heart disease, heart failure, cerebrovascular accidents or peripheral arterial disease were excluded. Hypertension was diagnosed in patients with a blood pressure of ≥140/90 mmHg and in those taking antihypertensive agents. Obesity was defined if body mass index (BMI) (calculated as weight in kilogrammes divided by height in squared metres) was greater than 30.

In all cases anti-TNF-α monoclonal antibody-infliximab was prescribed because of active disease. All patients included in the current study had be-

gun treatment with NSAIDs immediately after the disease diagnosis. All of them were still being treated with these drugs at the time of the study. At the time of this study most patients were on treatment with naproxen: 500-1000 mg/d. However, since the criterion for initiation of infliximab therapy was severe disease refractory to NSAIDs, all of them had been treated with at least 3 NSAIDs prior to the onset of infliximab therapy.

The main demographic, clinical and laboratory data of this series of AS patients are shown in Table I. Since at the time of the study all patients were undergoing periodical treatment with the anti-TNF-α monoclonal antibody-infliximab, the mean BASDAI was only 2.94±2.11. In this regard, BASDAI values were higher in all the patients before the first infusion of infliximab.

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 on the short-term effect of infliximab therapy on insulin resistance in RA (18) was supported by any pharmaceutical drug company.

Table I. Demographic, clinical and laboratory data of 30 patients with ankylosing spondylitis.

Variable	
Mean age (years) ±SD	
At the time of study	50.5 ± 14.8
At the time of onset of symptoms	28.2 ± 10.4
Delay to diagnosis (years) ±SD	11.5 ± 9.0
Men/Women	21/9
Mean disease duration (years) ±SD*	22.0 ± 13.2
History of classic cardiovascular risk factors	
Hypertension	12 (40.0%)
Dyslipidemia	11 (36.7%)
Obesity (BMI > 30 kg/m^2)	3 (10.0%)
Current smokers	13 (43.3%)
Mean blood pressure (mm Hg) ±SD*	
Systolic	123.2 ± 18.2
Diastolic	75.7 ± 12.5
Mean body mass index (kg/m^2) ±SD	26.7 ± 3.3
Mean BASDAI ±SD*	2.94 ± 2.11
Mean VAS ±SD*	31.1 ± 24.2
Hip involvement, n (%)	6 (20.0%)
Synovitis or enthesitis in other peripheral joints, n (%)	11 (36.7%)
Anterior uveitis, n (%)	6 (20.0%)
Syndesmophytes, n (%)	10 (33.3%)
Mean CRP (mg/l) ±SD**	
At the time of disease diagnosis	24.0 ± 33.4
At the time of study	6.2 ± 8.7
Mean ESR (mm/1st hour) ±SD***	
At the time of disease diagnosis	30.1 ± 28.2
At the time of study	19.0 ± 15.2
Mean cholesterol or triglycerides*	
Total cholesterol	199.1 ± 30.6
HDL cholesterol	53.2 ± 12.8
LDL cholesterol	126.8 ± 26.5
Triglycerides	94.0 ± 53.7
Mean fasting serum glucose (mg/dl) ±SD*	92.8 ± 8.6
HLA-B27 positive (n=27)	20 (74.1%)

At the time of the study*; **Normal value <5 mg/l; ***Normal value <20 mm/1st hour.

Study Protocol

In all cases, the drug was given as an intravenous infusion in a saline solution over 120 minutes. Blood samples were taken at 0800 hours (time 0) for the determination of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (latex immuno-turbidimetry), lipids (enzymatic colorimetry), plasma glucose, serum insulin serum insulin (μU/ml) levels (DPC, Dipesa, Los Angeles, CA, USA) immediately prior to an infliximab infusion. Also, blood samples for determination of plasma glucose and serum insulin were taken just at the end of infliximab infusion (time 120). None of the patients did receive any nutrient before and during infusion.

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 (19), and the quantitative insulin sensitivity check index (QUICKI) using the formula = 1/log insulin (μU/ml) + log glucose (mg/dl) (20). Although results on HOMA and QUICKI are shown in this report; the use of the QUICKI is superior to the HOMA index since the variables are logarithmically transformed (20). Patients with HOMA values ≥2.29 were classified as having insulin resistance as recommended in the literature (21).

Statistical analyses

Glucose, HOMA and QUICKI before (time 0) and postinfusion (time 120) were compared using the paired Student's *t*-test. Comparisons were adjusted by age, sex and BMI. Correlation between basal HOMA at time 0 with selected continuous variables was performed adjusting by age at the time of the study, sex, and classic cardiovascular risk factors via estimation of the Pearson partial correlation coefficient (r). Two-sided *p*-values ≤0.05 were considered to indicate statistical significance. Analyses were performed using Stata 12/SE (StataCorp, College Station, TX).

Results

At the time of the study only 8 (26.7%) of the 30 patients fulfilled definitions for insulin resistance as HOMA in-

Table II. Differences between basal (time 0) and postinfusion (time 120 minutes) glucose, HOMA, and QUICKI.

	Basal (time 0) Mean ± SD	Postinfusion (time120) Mean ± SD	*p*-value
Plasma glucose (mg/dl)	92.9 ± 9.2	89.3 ± 7.4	0.005
HOMA	1.72 ± 1.22	1.18 ± 0.94	<0.001
QUICKI	0.37 ± 0.04	0.39 ± 0.04	0.004

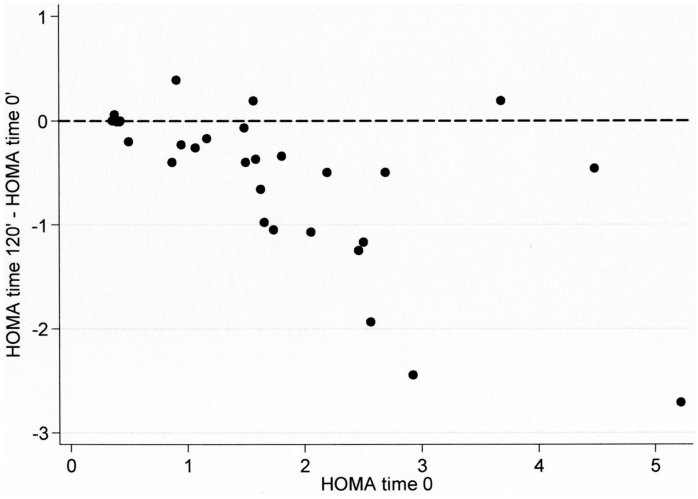

Fig. 1. Changes in HOMA index as function of HOMA basal values. Negative values indicate that HOMA index decreased after infusion of infliximab (at time 120). The figure shows that (1) HOMA decreased in most patients; (2) the higher the HOMA basal value, the greater the decrease after infliximab infusion was.

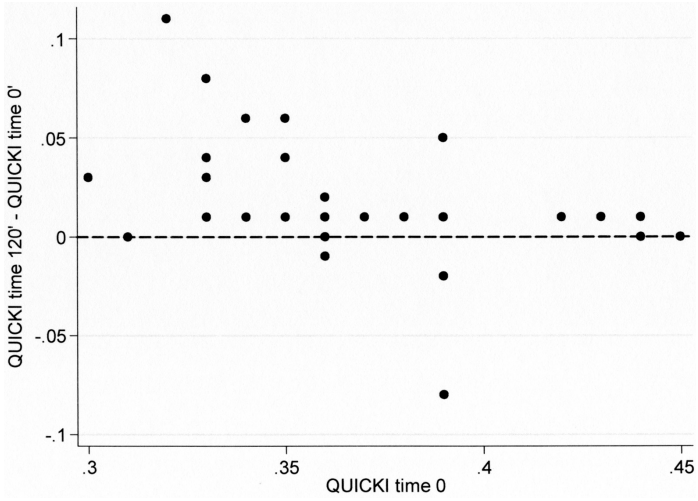

Fig. 2. Changes in QUICKI index as function of QUICKI basal values. Positive values indicate that QUICKI index increased after infusion of infliximab (at time 120). The figure shows that (1) QUICKI increased in most patients; (2) the higher the QUICKI basal value, the smaller the increase after infliximab was.

dex was in most cases less than 2.29. Nevertheless, a dramatic reduction in the serum insulin levels following infliximab infusion was found. Because of that, a statistically significant reduction in the HOMA values was observed when results found at time 0 were compared with those observed immediately after infliximab infusion (time 120) ($p<0.001$) (Table II). Figure 1 confirmed that HOMA decreased in most patients. The decrease in HOMA value was more important in those patients with the higher values of HOMA before infliximab infusion. Also, a significant improvement of insulin sensitivity was observed in most patients when QUICKI values before (time 0) and those observed postinfusion (time 120) were compared ($p=0.004$) (Table II). Figure 2 shows that the increase in QUICKI values at time 120 was smaller in those patients with higher QUICKI values at time 0.

A low QUICKI is known to be in keeping with insulin resistance. Apart from disease activity, obesity was found to contribute to insulin resistance in inflammatory arthritis (22). However, only 3 (10%) of the 30 patients from this series of non-diabetic AS patients had BMI greater than 30 (Table I). Because of that, no significant correlation between baseline HOMA and BMI was observed (Table III). Also, no significant correlation between ESR, CRP and BASDAI and HOMA at time 0 was observed (Table III).

Discussion

The present study shows that non-diabetic patients with AS on treatment with infliximab, which specifically and with high affinity binds to TNF-α and neutralises this cytokine, experience a rapid and dramatic reduction in the serum insulin levels and a rapid improvement of insulin sensitivity following administration of this drug.

In line with the above, Kiortsis *et al*. found a significant decrease of the HOMA index and increase of the QUICKI in AS patients with high insulin resistance after 6 months' treatment with infliximab (15). Since most of the AS patients assessed in our study were not obese and none of them had basal glucose levels greater than 110 mg/dl, the mean HOMA found in our series of patients was below the levels required to establish the presence of insulin resistance. On the other hand, the AS population analysed in the present study did not have a great disease activity measured by BASDAI at the time of the study. This might be another reason why patients had a low HOMA index (taking into account the relation of inflammation and endothelial dysfunction), apart from the low frequency of obesity and normal glucose levels. Nevertheless, our data were in keeping with those from Sari *et al*. that showed that in the absence of classic CV risk factors insulin levels and insulin resistance indices are similar in AS patients and controls (23).

Almost three decades ago Scandinavian investigators described the presence of glucose intolerance in patients with RA and other chronic inflammatory diseases (24). The degree of the impaired glucose handling was related to the severity of inflammatory activity as defined by acute phase reactants (24).

Table III. Partial correlation of basal HOMA-insulin resistance at time 0 with selected continuous variables adjusting by age at the time of the study, sex, and classic cardiovascular risk factors in 30 patients with ankylosing spondylitis.

	r-value	*p*-value
Age at the onset of symptoms	0.1358	0.50
Disease duration*	-0.1345	0.50
BMI*	0.2532	0.20
BASDAI*	0.3483	0.08
VAS*	0.1629	0.42
ESR at the time of disease diagnosis (natural-log-transformed)	-0.0714	0.72
CRP at the time of disease diagnosis (natural-log-transformed)	-0.0580	0.77
ESR at the time of the study (natural-log-transformed)	0.0332	0.87
CRP at the time of the study (natural-log-transformed)	0.0465	0.82

*At the time of the study.

In patients with active RA the impaired glucose handling combined with hyperinsulinemia was directly related to peripheral insulin resistance (25). 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 (26).

Dessein *et al*. reported that the acute phase response predicts insulin resistance in RA (27). In a former study we described a rapid and dramatic decrease of HOMA index as well as a rapid increase of QUICKI following infliximab infusion in long standing RA patients undergoing TNF-α antagonist therapy due to severe disease (18). However, in contrast to the present series of infliximab-treated AS patients, the inflammatory burden of that series of RA patients was more severe. Because of that, the mean basal HOMA level of the RA patients was greater than 2.29 (mean: 3.4) (18) while the mean value in this series of AS patients was only 1.72. These observations support the former conclusions raised by Dessein *et al*. (27) and highlight the role of the severity of the inflammatory response in the complex mechanisms leading to the development of metabolic syndrome in patients with chronic inflammatory diseases.

TNF-α production is increased under chronic hyperglycemia and TNF-α has ominous effects on insulin sensitivity (28). 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 (29). TNF-α directly impedes insulin-glucose mediated uptake in the skeletal muscle (29).

Together with previous reports, our observations may suggest that anti-TNF-α blockade in patients with AS has concurrent beneficial effects on disease activity (13), endothelial dysfunction (12), and insulin sensitivity. These positive effects may be implicated in the reduction of CV complications observed in patients with rheumatic disease undergoing anti-TNF-α therapy.

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