both rheumatoid arthritis and ulcerative colitis 2 weeks after a normal delivery.⁴

Accordingly, this case suggests the contribution of the anti-aromatase treatment. In this case, additional factors such as the presence of the shared epitope could explain the switch from common benign arthralgias to active destructive rheumatoid arthritis. At the late stage, cessation of treatment had no effect on arthritis. The presence of erosions suggests that the patient had rheumatoid arthritis with low disease activity, which became worse when aromatase inhibitors were used. Accordingly, arthralgias in women receiving aromatase inhibitors should be better evaluated to estimate the incidence of rheumatoid arthritis.

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Competing interests: None declared.

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Accepted 2 November 2006

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Improved insulin sensitivity by anti-TNF α antibody treatment in patients with rheumatic diseases

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Ann Rheum Dis 2007;**66**:558–559. doi: 10.1136/ard.2006.062323

Insulin resistance is a key factor in the pathogenesis of the metabolic syndrome and type 2 diabetes, but the underlying mechanisms remain poorly understood. Adipocytokines, including tumour necrosis factor α (TNF α), interleukin 6, leptin and adiponectin,^{1,2} are increasingly recognised as important regulators of both insulin sensitivity, as well as inflammation, and a dysregulation of their levels and/or functions has been shown in both obesity and rheumatoid arthritis.³ Further investigations have substantiated the important negative effects of TNF α on insulin-mediated glucose uptake and the development of insulin resistance.⁴ In this study, the influence of therapeutic TNF α blockade on insulin

sensitivity was investigated in regularly treated patients with rheumatic diseases.

A group of eight patients who were non-diabetic and having various chronic inflammatory disorders (table 1) were investigated in an open prospective study design. Patients were attending the outpatient clinic of the Sint Maartenskliniek in Nijmegen and entered the study after giving their written informed consent. The regional medical ethical committee approved the study. Patients started the treatment with infliximab (3 mg/kg) and were followed up over a period of 6 weeks. During this interval, the additional antirheumatic drugs remained unchanged. Table 1 gives the patient characteristics.

Table 1 Characteristics of study participants

Patient number	1	2	3	4	5	6	7	8	Mean (SEM)
Age (years)	65	38	70	57	54	34	61	43	53 (5)
Sex	M	M	M	M	M	F	M	M	M:F=7:1
Diagnosis	RA	RA	RA	RA	Wd	RA	AS	AS	
Disease duration (years)	7	4	14	10	3	8	26	22	
RF	+	–	+	+	NA	+	NA	NA	
DAS28 I	5.26	4.28	7.65	3.75	4.25	3	NA	NA	4.7 (0.7)
DAS28 II	2.75	1.09	5.40	2.68	4.43	2.25	NA	NA	3.1 (0.6)
ESR I (mm/h)	36	14	43	37	38	10	67	14	32 (7)
ESR II (mm/h)	26	3	25	18	56	6	15	5	19 (6)
Prednisone	Yes	No	Yes	No	Yes	Yes	No	Yes	
DM2 in family	No	Yes	No	No	No	Yes	No	Yes	
Glucose (mmol/l)	7.5	5.2	4.9	4.3	4.6	5.7	4.9	4.8	5.2 (0.4)
BMI (kg/m ²)	27	25	24.3	22	28.1	22.4	26	24.5	24.6 (0.7)
Δ M(mg/kg/min)	0.12	2.79	1.33	4.28	0.06	3.46	–1.13	0.17	0.75 (5.41)

AS, ankylosing spondylitis; BMI, body mass index; DAS28 I/II, disease activity score at baseline (I) and after 6 weeks (II); DM2, type2 diabetes mellitus; ESR I/II, erythrocytes sedimentation rate at baseline (I) and after 6 weeks (II); F, female; M, male; Δ M, variation of insulin sensitivity, as assessed by M value; –, minus; NA, not available; +, plus; RA, rheumatoid arthritis; RF, rheumatoid factor; Wd, Whipple's disease.

Results are expressed as mean (SEM), except for Δ M where they are presented as median (range).

Figure 1 (A) Effects of anti-tumour necrosis factor (TNF) therapy on insulin sensitivity. M values were calculated as the average glucose infusion rate during the last 30 min, the plateau phase, of the clamp.^{5,6} The lowest limit of normal values was derived from previous studies of our group in healthy volunteers^{5,6} and corresponds to 5.8. Black lines represent the median, whereas the dotted line represents the lowest normal limit. CS, patients receiving oral corticosteroids (Wilcoxon test was used). (B) Relationship between BMI at baseline and the change in insulin sensitivity after therapeutic TNF α blockade. ΔM =variation of M value between the two time points investigated (Spearman's t test was used).

Hyperinsulinaemic–euglycaemic clamps were performed as described in detail elsewhere^{5,6} before each anti-TNF infusion, and the M value was used to quantify insulin sensitivity.^{3,6} At baseline, two patients with rheumatoid arthritis had both a higher fasting glucose concentration and a slight decrease in insulin sensitivity, and an additional four had low-insulin sensitivity. This suggests that our group of patients were characterised by insulin resistance, which is in line with previous reports.³ Although, TNF α neutralisation was previously reported to fail to improve insulin sensitivity in obese non-insulin dependent patients with diabetes,⁷ in this study, it improved insulin sensitivity in seven patients (5.09 (6.24) at baseline vs 6.56 (8.97) after 6 weeks, $p = 0.05$), restored insulin sensitivity within the normal ranges in three patients, whereas TNF neutralisation slightly worsened insulin sensitivity in one patient (fig 1A) who had ankylosing spondylitis and manifestations of peripheral arthritis (table 1). Our findings are in line with previous studies, which reported that anti-TNF agents corrected disturbances in glucose metabolism in patients with rheumatoid arthritis.^{8,9} To our knowledge, our study is the first to apply hyperinsulinaemic–euglycaemic clamps, the gold standard method for assessing insulin sensitivity, in documenting this effect.

During our study, except for one patient who later turned out to have Whipple's disease, TNF α neutralisation was accompanied by a considerable decrease in DAS28 and ESR (table 1). We therefore hypothesised that the suppression of the inflammatory cascade might be responsible for the improvement of observed insulin sensitivity.⁴ However, no significant correlation between disease activity or other inflammatory markers and insulin sensitivity at both time points could be detected. Interestingly, the improvement in insulin sensitivity correlated negatively with the baseline BMI ($r = -0.83$, $p = 0.01$) in our study (fig 1B). This finding was unexpected and an explanation for that is currently under investigation in our laboratory.

In conclusion, using the hyperinsulinaemic–euglycaemic clamp technique, we found that TNF α blockade in patients with chronic inflammatory conditions improves insulin sensitivity, which is likely to be mainly due to the reduction of the inflammatory status. This change may decrease long-term cardiovascular risk in rheumatoid arthritis.

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Accepted 10 October 2006

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