No change of serum levels of leptin and adiponectin during anti-tumour necrosis factor antibody treatment with adalimumab in patients with rheumatoid arthritis

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Leptin and adiponectin, two fat tissue hormones, are increased or tend to be increased in patients with rheumatoid arthritis (RA).[1 2] They are likely to be stimulated by proinflammatory cytokines such as tumour necrosis factor (TNF),[3 4] and both were found to be increased in the synovial fluid of patients with RA.[1 2] Thus, one would expect lowering of serum levels of these two hormones during anti-TNF antibody treatment.

As part of a recently published study with adalimumab (Abbott SpA, Campoverde di Aprilia, Italy),[5] we included 32 white patients with RA (30 postmenopausal women, two men) fulfilling the American College of Rheumatology criteria for RA.[6] The patients were selected according to the inclusion criteria of the adalimumab Research in Active RA study (ReAct). A total of 16 patients (15 female, one male) did not receive parallel or prior (6 months before) prednisolone treatment. The other 16 patients (15 female, one male) received prednisolone treatment (mean (SEM) 4.6 (0.2) mg/day). The initial mean (SEM) body mass index in the two groups was 22.8 (0.8) kg/m^2 (without prednisolone) and 22.3 (0 8) kg/m^2 (with prednisolone). We did not see any obvious change of body weight throughout the study. All patients were given additional methotrexate (stable throughout this study) but no other immunosuppressive drugs. Patients were assigned to receive single self-injections of adalimumab subcutaneously at 40 mg every other week. A baseline blood sample was taken 1–2 weeks before the start of adalimumab treatment. Anti-TNF antibodies were infused on weeks 0, 2, 4, 6, 8, 10, and 12. For this study, patients were clinically investigated and blood was drawn between 8 am and 9 am when the patients visited the outpatient clinic on the baseline day and at weeks 2, 6, and 12. The blood was immediately centrifuged and serum was stored at −80℃. The study was approved by the ethics committee of L Sacco University Hospital, Italy.

We used enzyme immunometric assays for the quantitative determination of serum levels of leptin (IBL, Hamburg, Germany), adiponectin (R&D Systems, Wiesbaden, Germany), and interleukin (IL)6 (R&D Systems). Intra-assay and inter-assay coefficients of variation for all tests were <10%.

Table 1 shows that during 12 weeks of adalimumab treatment in patients, with and without prednisolone, typical measures of inflammation markedly decreased. This indicates that adalimumab was effective in reducing RA associated inflammation. However, serum levels of leptin and adiponectin did not change during adalimumab treatment (fig 1). Interestingly, although having similar body mass indices, patients with prior prednisolone treatment had markedly decreased serum levels of adiponectin in comparison with patients without glucocorticoids (fig 1). This difference remained constant throughout the observation period (fig 1).

In this study, we expected a decrease of serum levels of leptin and adiponectin in patients with RA receiving adalimumab treatment because both hormones are thought to be stimulated by proinflammatory cytokines such as TNF.[3 4] We do not believe that an increase of body fat mass has masked a leptin fall because not one anti-TNF treatment study has reported a dramatic effect on body fat mass (even in inflammatory bowel diseases). In addition, others did not find a correlation between serum levels of leptin and disease activity in patients with RA and juvenile arthritis,[7 8] which may demonstrate that in these patients the link between inflammation and serum levels of leptin is probably not strong. This finding was later confirmed by another group.[9] Others have demonstrated that serum leptin levels are inversely correlated with markers of inflammation such as C reactive protein.[10] In our study we did not find any correlation between serum levels of leptin or adiponectin and the number of swollen joints or tender joints, serum IL6, C reactive protein (data not shown, but p values are >0.2). However, adiponectin levels were lower in the patients with RA who had been treated with prednisone; the reason for this is presently unknown.

In conclusion, in patients with RA, serum levels of leptin and adiponectin are not linked to inflammation and are not down regulated by 12 weeks of anti-TNF treatment.

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Table 1 Course of response measures during 12 weeks of adalimumab treatment

Time	Swollen joints* (n)	Tender joints* (n)	Patient's global assessment of pain* (VAS)	IL6 serum levels* (pg/ml)
Baseline	8.8 (0.7) {9.1 (0.6)}	10.5 (0.8) {9.5 (0.5)}	54.8 (4.5) {54.8 (3.7)}	21.6 (7.4) {33.9 (12.2)}
Week 2	7.3 (0.9) {7.0 (0.7)}	9.6 (0.7) {8.1 (0.5)}	40.8 (3.5) {40.7 (5.3)}	4.1 (1.8) {7.0 (1.8)}
Week 6	4.3 (0.9) {4.3 (0.6)}	7.5 (0.80) {6.5 (0.7)}	32.3 (3.8) {38.5 (3.8)}	8.7 (5.3) {5.5 (2.1)}
Week 12	2.8 (0.5) {3.4 (0.6)}	6.1 (0.5) {5.4 (0.7)}	23.3 (3.7) {25.2 (4.7)}	2.9 (0.9) {13.8 (8.5)}

Data of patients with prednisolone treatment are given in {brackets}. Data are given as means (SEM).
*p<0.003 indicating a decrease as assessed by the Friedman test.

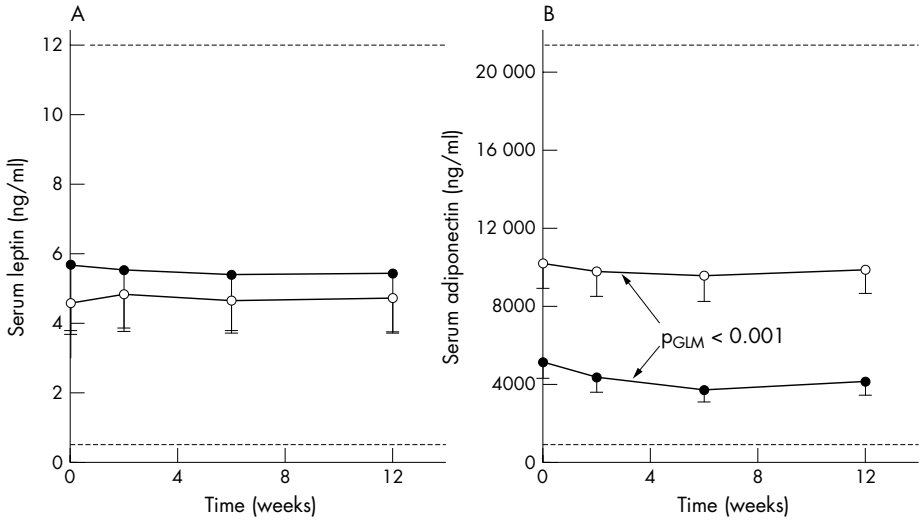

Figure 1 Course of serum levels of leptin (A) and adiponectin (B) in patients with RA with (black symbols) and without (white symbols) prednisolone treatment. A comparison of the two groups in (B) was carried out using the general linear model (GLM) statistical technique. The Friedman test indicated no significant change during the course of adalimumab treatment. The dashed lines indicate lower and upper limits of the normal range in women. Data are given as means (SEM).

Conflict of interest: None.

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Mycophenolate mofetil for lupus related myelopathy

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Myelopathy is a rare manifestation of systemic lupus erythematosus (SLE). The standard treatment consists of high dose corticosteroids and intravenous pulse cyclophosphamide (CYC).[1 2] Despite this, our previous experience indicated that half of the patients with lupus related myelopathy did not respond completely to CYC treatment.[3] Moreover, toxicities of CYC are of major concern, particularly severe infections and ovarian failure.[4] Therefore, less toxic or more effective alternative treatments are needed.

Mycophenolate mofetil (MMF) is a relatively new immunosuppressive agent that has increasingly been used in patients with SLE because of its favourable efficacy and safety.[5] Controlled trials have confirmed its efficacy in the induction and maintenance treatment of proliferative lupus nephritis.[6 7] MMF has also been reported to be useful in refractory multiple sclerosis.[8] However, information about the efficacy of MMF in neuropsychiatric SLE is scant. We here report our preliminary experience of the use of combined corticosteroid and MMF in the treatment of lupus related myelopathy.

Three patients who fulfilled the 1982 American College of Rheumatology criteria for SLE and had acute myelopathy were treated with a protocol consisting of high dose corticosteroids (daily intravenous methylprednisolone pulses (15 mg/kg) for 3 days, followed by oral prednisolone 0.6 mg/kg/day for 6 weeks, then tapered by 5 mg/week until <10 mg/day) and MMF (2 g/day for 6 months, followed by 1 g/day in two divided doses). Intravenous immunoglobulin for one course (5 days of 0.4 g/kg) could be given as rescue treatment if the response was suboptimal. Rehabilitative