Anti-TNF therapy in rheumatoid arthritis: Searching for mechanisms of effect
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Treatment-specific changes in circulating adipocytokines: a comparison between tumour necrosis factor blockade and glucocorticoid treatment for rheumatoid arthritis


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ABSTRACT

Objective
There is increasing evidence that adipocytokines may exert pro-inflammatory and destructive effects in rheumatoid arthritis (RA). Hence, we investigated the relationship between adipocytokines and several features associated with RA (inflammation, joint destruction and cardiovascular disease), as well as the effect of treatment with a tumour necrosis factor (TNF) inhibitor or glucocorticoïds (GC) hereupon.

Methods
Serum levels of adiponectin, leptin, resistin, visfatin, vaspin and lipids were determined in a well-defined cohort of RA patients before and after 16 weeks of adalimumab treatment (adalimumab cohort). The same parameters were analysed in two other RA patient cohorts before, and after 2 weeks of high-dose prednisolone (high GC cohort) and before and after 22 weeks of treatment with a combination regimen with tapered high-dose prednisolone (COBRA-GC cohort). Radiographs of hands and feet (adalimumab and COBRA-GC cohorts) were assessed at baseline and after therapy.

Results
Treatment with adalimumab or GC showed opposing effects on vaspin and visfatin levels. Lipid levels improved after several months of adalimumab or GC treatment; in the adalimumab cohort, this was related to reduced visfatin levels, independent of C-reactive protein (CRP) levels. After long-term adalimumab or GC treatment, resistin levels declined, which was associated with a decrease in inflammation markers. In the adalimumab cohort, baseline resistin levels were predictive of baseline radiological damage, independent of anti-citrullinated peptide antibodies (ACPA) status or CRP levels.

Conclusion
Changes in serum adipocytokine levels were treatment-specific, further strengthening the role of visfatin and resistin in several disease manifestations of RA.
INTRODUCTION

In rheumatoid arthritis (RA) synovitis may lead to progressive destruction of articular cartilage and subchondral bone\(^1\). In addition, systemic inflammation, a hallmark of RA, is thought to play a key role in accelerated atherosclerosis, explaining the link between RA and an increased incidence of cardiovascular disease (CVD)\(^2\). White adipose tissue cells can influence immune functions and inflammatory processes in conditions like RA by secretion of adipocytokines as well as classic cytokines\(^3\),\(^4\) and these mediators have provided a plausible link between obesity, inflammation and CVD\(^5\),\(^6\). Increased serum adipocytokine levels in patients with active RA\(^7\) could perhaps be associated with the occurrence of accelerated atherosclerosis and CVD, and are thought to play a role in the development of bone erosions\(^7\)-\(^13\).

Tumour necrosis factor (TNF) blockade does not only improve clinical signs and symptoms in RA\(^14\), but also protects against progressive joint destruction\(^15\) and reduces the risk of first-ever CVD events\(^16\),\(^17\). Of interest, we have recently shown that a high baseline body mass index (BMI) was related to less erosive disease at presentation, but also to a diminished clinical response to anti-TNF treatment with infliximab in established RA patients\(^18\). These data support the notion that fat tissue may play a role in RA pathogenesis. Glucocorticoids (GCs) effectively reduce synovitis\(^19\),\(^20\). However, high-dose GC (≥7.5 mg daily) is known to be associated with CVD complications, such as atherosclerosis, in RA\(^22\),\(^23\).

Although TNF inhibitors and GCs both reduce synovitis, high doses of the latter do not reduce the risk of CVD, which could indicate a different regulation of adipocytokines is at play.

To provide insight into the role of adipocytokines in RA, we investigated the adipocytokine serum levels in relationship to the acute phase response, radiological damage, and lipid profile. In addition, we studied the effect of different anti-rheumatic treatments on serum adipocytokines in three different cohorts of RA patients, who started treatment with either adalimumab or different regimens of GC treatment.

PATIENTS AND METHODS

Patients from all cohorts fulfilled the 1987 American College of Rheumatology (ACR) classification criteria for RA\(^24\) and had active disease as defined by a disease activity score evaluated in 28 joints (DAS28) ≥3.2. The studies were performed according to the Declaration of Helsinki and all three cohorts were approved by the medical ethics committee and all participants gave written informed consent.

Adalimumab cohort

Baseline demographic and clinical features of patients from the larger open-label, prospective, single-centre adalimumab cohort have been previously described\(^25\). Forty-eight patients were included for the present analysis, based on the availability of serum at baseline and after 16 weeks combined with standardized follow-up data on the response to adalimumab treatment. All patients received 40 mg adalimumab subcutaneously every 2 weeks, in combination with a stable methotrexate (MTX) dose for at least 16 weeks. Use of oral GCs (prednisone ≤10 mg/day)
was allowed. Clinical response at 16 weeks was determined according to the European League Against Rheumatism (EULAR) response criteria

**High-dose glucocorticoid cohort**

Nine patients from the active arm of a previously conducted, double-blind, randomised, placebo-controlled trial were treated with 60 mg of oral prednisolone daily for 1 week followed by 40 mg prednisolone daily during the second week serum adipocytokine levels were measured at baseline and after 2 weeks. One patient of the original cohort was excluded due to an insufficient amount of stored serum. In this study, response was defined as a decrease in DAS28 ≥1.2 after 2 weeks of GC treatment.

**COBRA glucocorticoid cohort**

Twenty-one patients were treated according to the 40-week, intensified COBRA trial as described earlier. Serum was sampled at baseline and after 21 weeks of treatment and directly stored at -20°C. For the current study, samples of 19 patients were available and analysed for adipocytokine. Response was determined according to the EULAR response criteria.

**Adipocytokine assays**

Serum adiponectin, leptin and resistin were analysed using a multiplex immunoassay for human adipocytokine profiling, as previously described. Commercially available, quantitative sandwich ELISAs were used to determine serum levels of visfatin (Biovision, Mountain View, CA, USA) and vaspin (AdipoGen, San Diego, CA, USA). Visfatin ELISA results from three patients were excluded from further analysis, because they were outside of assay range. To avoid possible confounding effects of RF, all samples for the multiplex immunoassay were pre-incubated with protein L (Pierce, Rockford, IL, USA) and residual immunoglobulins were blocked with equal volume of 10% (v/v) normal rat and mouse serum (Rockland, Gilbertsville PA, USA, as previously described.

For the vaspin and visfatin ELISAs, three randomly selected samples of RF-negative RA patients were spiked with freeze dried RF (200 IU/ml) in a 1:1 or 1:3 ratio. Samples demonstrated high recovery across the concentration range and we concluded serum RF did not interfere with vaspin or visfatin assessments (data not shown).

**Lipid profiles and assessment of radiological damage**

Blood was drawn from patients while fasting at the specified time points as described above. Lipid levels were measured using standard laboratory techniques. Radiographs of the hands and feet were obtained at baseline and after 1 year (adalimumab cohort) or 40 weeks (COBRA cohort) of treatment and were scored using the Sharp/van der Heijde score (SHS). No X-rays were available for the high-GC cohort.

**Statistical analysis**

Continuous data were described as mean (SD), if normally distributed, or median (interquartile range [IQR]), if not normally distributed. The unpaired Student’s t-test or, where appropriate, Mann-Whitney U test was used to compare responders and non-responders. Categorical data
were represented as n (%) and analysed using the Chi-square or Fisher’s exact test. Correlations were assessed with the Pearson product-moment or Spearman rank-order correlation coefficients. A paired Student’s t-test or Wilcoxon signed-rank test was used to determine significant changes from baseline within groups. Linear regression analysis was used to test if levels of the different adipocytokine were related to SHS; SHS was log-transformed to fit this model. Multivariate linear regression analysis was performed to study the influence of other variables at baseline on baseline SHS score. In a linear regression analysis, visfatin (or change in visfatin) and CRP (or change in CRP) were used as independent variables to assess their influence on, respectively, TC/HDL, HDL/LDL or apo B/A-I ratios (or change in these above mentioned ratios.) All statistical analyses were performed with SPSS v16.0 for Windows (SPSS, Chicago, IL, USA). A p-value of ≤0.05 was considered statistically significant.

RESULTS
Baseline patient characteristics and clinical response to treatment
The baseline patient characteristics of the adalimumab cohort are summarised in Table 1. Sixteen weeks after initiation of treatment, mean (SD) DAS28 decreased from 5.5 (1.1) at baseline to 3.6 (1.2) (p <0.001). All baseline patient characteristics were tested for differences between EULAR responders and non-responders; no significant differences were found (Table 1). For the high-GC and COBRA-GC cohorts, baseline patient characteristics are shown in Table 2. In the high-GC cohort the mean (SD) DAS28 decreased from 6.2 (1.0) to 3.6 (1.5) after 2 weeks (p = 0.008). In the COBRA-GC cohort, there was a mean (SD) reduction in DAS28 from 5.3 (0.9) to 2.1 (1.3) after 21 weeks (p < 0.001, compared with baseline).

Pre-treatment adipocytokine serum levels are not associated with DAS28
In the adalimumab cohort, serum levels of the different adipocytokines were not correlated with CRP, ESR or DAS28 at baseline with the exception of adiponectin. Adiponectin was inversely associated with CRP, ESR and DAS28 at baseline (respectively r = -0.31, p = 0.04; r = -0.33, p = 0.02 and r = -26, P = 0.08). Only leptin, and none of the other four adipocytokines, was positively correlated with BMI (r = 0.47, p = 0.001). No differences or correlations in serum adipocytokine levels were found between ACPA- and/or RF-positive RA patients and age. In the high-GC cohort and the COBRA-GC cohort, adipocytokines were not related to age, DAS28, CRP or ESR or ACPA at baseline. In the COBRA-GC cohort RF was positively correlated to visfatin (r = 0.58, P = 0.01) and leptin (r = 0.58, P = 0.014). In the high-GC cohort a negative association was found between RF and visfatin (r = -0.775, P = 0.04).

Adalimumab treatment leads to a decrease in resistin and visfatin serum levels, but only resistin decline is associated with disease activity reduction
Median [IQR] levels of visfatin (2.6 [1.5-3.3] to 1.6 [1.0-2.7] ng/mL, p = 0.004) and resistin (24 [18-30] to 20 [14-26] ng/mL, p = 0.008) showed statistically significant decreases after 16 weeks of adalimumab treatment compared with baseline (Figure 1A). Similar changes
were observed after adalimumab treatment in the subgroup of 33 patients who did not use concomitant prednisolone (data not shown). Leptin, adiponectin and vaspin serum levels showed no statistically significant changes after 16 weeks of treatment with adalimumab (Figure 1A). Visfatin and resistin decreased significantly only in EULAR responders (p = 0.002 and p = 0.004, respectively; Figure 1B); in EULAR non-responders, none of the adipocytokines showed significant changes (Figure 1C).

The decrease in resistin was significantly and positively correlated to the decrease in DAS28, CRP and ESR after 16 weeks (r = 0.38, p = 0.009; r = 0.34, p = 0.02; r = 0.32, p = 0.03, respectively), but not for visfatin (data not shown). None of the baseline adipocytokine levels predicted later clinical response to adalimumab, even after adjustment for gender and BMI (data not shown).

Vaspin serum levels increase and resistin levels decrease after glucocorticoid treatment
Short-term treatment with high-dose GC (high-GC cohort) resulted in significant median [IQR] increases of adiponectin, leptin and vaspin serum levels 2 weeks after start of therapy.
Table 2 Baseline patient characteristics of glucocorticoid and COBRA cohort

<table>
<thead>
<tr>
<th></th>
<th>GC cohort (n = 9)</th>
<th>COBRA cohort (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>52 (8)</td>
<td>51 (14)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5 (56%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.3 (1.0)</td>
<td>5.3 (0.9)</td>
</tr>
<tr>
<td>Erosive disease, n (%)*</td>
<td>8 (89%)</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>RF, n (%)</td>
<td>5 (71%)</td>
<td>13 (72%)</td>
</tr>
<tr>
<td>ACPA, n (%)</td>
<td>4 (57%)</td>
<td>13 (75%)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>45 (18-80)</td>
<td>34 (26)</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>15 (4-60)</td>
<td>16 (8-30)</td>
</tr>
<tr>
<td>Disease duration (mo)</td>
<td>10 (6-29)</td>
<td>3.2 (4.4)</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>39 (13-120)</td>
<td>12 (10-37)</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>31 (24-39)</td>
<td>16.9 (13.5-22.0)</td>
</tr>
<tr>
<td>Adiponectin (mg/mL)</td>
<td>72 (43-91)</td>
<td>15.7 (15.2-16.3)</td>
</tr>
<tr>
<td>Visfatin (ng/mL)</td>
<td>5.6 (4.3-7.7)</td>
<td>1.4 (1.1-3.7)</td>
</tr>
<tr>
<td>Vascin (ng/mL)</td>
<td>0.30 (0.22-0.64)</td>
<td>0.51 (0.16-0.72)</td>
</tr>
</tbody>
</table>

Data are represented as mean (SD), median (interquartile range [IQR]) or n (%), as appropriate. Baseline values of rheumatoid arthritis patients treated with an oral glucocorticoid (60 mg prednisolone daily for 1 week followed by 40 mg prednisolone daily for 1 week; GC cohort), or combination of oral dosages of hydroxychloroquine (400 mg/day), sulfasalazine (2 g/day), MTX (10 mg/week) and step-down high-dose prednisolone (tapered in 6 weeks from 60 to 7.5 mg/day [thereafter until end of trial]; COBRA cohort). Presence of erosive joint disease was determined by X-ray. Presence of IgM-RF was defined as serum levels ≥12.5 IU/mL for the GC cohort and ≥30 IU/mL for the COBRA cohort. BMI = body mass index; DAS28 = disease activity score evaluated in 28 joints; RF = IgM rheumatoid factor; ACPA = anti-citrullinated peptide antibodies; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein. ND = not determined.

compared with baseline (adiponectin 72 [43-91] to 88 [62-122] mg/mL, p = 0.012; leptin 39 [13-120] to 53 [17-190] ng/mL, p = 0.025; visfatin 0.30 [0.22-0.64] to 1.01 [0.61-2.00] ng/mL, p = 0.008; Figure 2A). Viscatin and resistin levels did not change significantly (Figure 2A).

Similar to short-term usage, long-term GC treatment (COBRA-GC cohort) showed a significant increase in median [IQR] visfatin levels after 21 weeks compared with baseline (0.51 [0.16-0.72] to 0.83 [0.41-1.50], p = 0.02) and no change in visfatin levels (Figure 2B). However, adiponectin and leptin levels were not affected by long-term GC treatment (COBRA-GC cohort). Interestingly, the mean (SD) serum resistin level decreased from 16.9 (13.5-22.0) at baseline to 13.5 (9.9-19.0) ng/mL after 21 weeks (p = 0.03); this 21-week decrease was associated with an ESR decline after 21 weeks (r = 0.51, p = 0.03). In both GC cohorts no association was found between change in any of the adipocytokines, and decrease in CRP, ESR or DAS28. None of the adipocytokines predicted response.

Decrease in visfatin serum levels is associated with improved lipid profiles after adalimumab treatment

In a previous analysis of the adalimumab cohort, we observed an improvement in the lipid profile⁸. Viscatin levels at baseline were positively correlated to the TC/ HDL (atherogenic index) and LDL/HDL ratios (respectively, r = 0.30, p = 0.05; r = 0.35, p = 0.02); these associations were independent of baseline CRP (data not shown). Furthermore, baseline adiponectin levels
were positively correlated to HDL levels ($r = 0.62, p < 0.001$), and negatively correlated to the atherogenic index ($r = -0.39, p = 0.006$) at baseline.

The decrease in serum visfatin levels was correlated with improved atherogenic index ($r = 0.35, p = 0.02$) and LDL/HDL ($r = 0.31, p = 0.04$) ratios after 16 weeks of adalimumab treatment (Figure 3). In a multivariate linear regression analysis, these associations were independent of decrease in CRP levels (visfatin change: $B = 0.092, 95\% \text{ CI} = 0.003-0.18; p = 0.04$). Serum resistin, leptin and vaspin were not associated with baseline lipid levels or changes in lipids after 16 weeks of treatment.

Similar to the adalimumab cohort, there was an improvement in the mean (SD) lipid index in the COBRA-GC cohort from baseline to 21 weeks (3.3 (0.77) to 2.8 (0.60), $p<0.001$). In contrast to the adalimumab cohort, there were no associations between baseline (or changes in) lipid levels (TC, HDL and TC/HDL) and any of the baseline (or changes in) adipocytokine levels in the COBRA-GC cohort.

**Resistin serum levels are associated with more radiological damage at baseline in the adalimumab cohort**

Higher resistin levels at baseline were associated with a higher baseline SHS in the adalimumab cohort ($R^2 = 12\%, p = 0.01$). A multiple regression analysis with as independent variables...
resistin, ACPA status and disease duration showed that disease duration ($p = 0.002$) and resistin ($p = 0.04$) independently predicted radiological damage (adjusted $R^2 = 26\%$). ACPA status did not predict SHS at baseline in this cross-sectional analysis. When CRP was added to the model as a fourth variable, disease duration ($p = 0.008$), CRP ($p = 0.01$) and resistin ($p = 0.055$) predicted

**Figure 2.** Changes in adipocytokine serum levels after short- or long-term glucocorticoid treatment. Serum levels of visfatin, resistin, vaspin, adiponectin and leptin from rheumatoid arthritis patients were measured at baseline and after treatment. (A) Individual changes after 2-week treatment with an oral glucocorticoid (60 mg prednisolone daily for 1 week followed by 40 mg prednisolone daily for 1 week; GC cohort) compared with baseline are shown. Wilcoxon signed rank test was used to compare the changes for each adipocytokine. Median (IQR) change (expressed as percentage) (B) after 21 weeks of combination treatment with oral dosages of hydroxychloroquine (400 mg/day), sulfasalazine (2 g/day), MTX (10 mg/week) and step-down high-dose prednisolone (tapered in 6 weeks from 60 to 7.5 mg/day [thereafter until end of trial]; COBRA cohort) compared with baseline value; Wilcoxon signed rank test was used. $^*p = 0.03$, $^{**}p = 0.02$. 

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radiological damage at baseline (adjusted $R^2 = 35\%$). The addition of BMI, concomitant low-dose prednisolone use at baseline or gender had no influence on this model. Baseline levels of the other adipocytokines did not predict joint destruction.

In the COBRA-GC cohort, a statistically significant mean (SD) SHS increase from 3.5 (0.5-10) to 5.3 (0.8-12.4) after 40 weeks was observed ($p < 0.005$). Neither baseline nor change in serum adipocytokine levels was associated with baseline or change in SHS.

**DISCUSSION**

We examined the levels of adipocytokines in relationship to inflammation, lipid profile, and radiological damage in three cohorts of RA patients initiating anti-rheumatic treatment. TNF blockade or GC showed opposing effects on vaspin and visfatin serum levels: GC treatment (both short- and long-term) increased vaspin, but not visfatin, while adalimumab led to decreased visfatin levels and had no effect on vaspin. The lipid profile improved after adalimumab or long-term GC treatment; in the adalimumab cohort, this was related to a visfatin reduction independent of CRP levels. After several months of treatment with adalimumab or prednisolone, we observed a decline in resistin levels, associated with a decrease in DAS28, CRP and ESR, or ESR only, respectively. In the adalimumab cohort, serum resistin levels at baseline were predictive of radiological damage at baseline, independent of ACPA status or CRP.

As a main finding we found a highly significant decrease in visfatin levels after adalimumab treatment, but not after GC treatment. In the adalimumab cohort, the baseline lipid profile and the subsequent improvement after treatment were related to the baseline serum visfatin level and decrease in visfatin concentrations, respectively. This latter relationship was independent
of CRP levels, suggesting a role for visfatin specifically in the improvement of the lipid profile independent of a decrease in disease activity. Visfatin serum levels are also increased in patients with diabetes mellitus or hypertension, and independently associated with increased CVD risk. The lipid profile improved not only after treatment with adalimumab, but also after treatment with GC in the COBRA-GC cohort. This effect has previously been ascribed to the decrease in inflammation after effective treatment.

Another interesting finding in this study is the increase of vaspin levels in GC-treated patients, which were unaffected after adalimumab treatment. Increased vaspin levels are associated with decreased insulin sensitivity, which is commonly seen after GC treatment. Vaspin could, therefore, also be involved in the opposing effects of anti-TNF and GC treatments on CVD risk.

After several months of treatment with either adalimumab or prednisolone, there was a decline in resistin levels, associated with a decrease in DAS28, CRP and ESR, or ESR only, respectively. These results are consistent with previous reports showing that serum resistin levels are correlated with markers of inflammation in RA patients. We are the first to report altered resistin levels after long-term treatment with GC. As resistin is mainly produced by macrophages and a decrease in the number of macrophages in synovium is consistently associated with improvement after effective treatment in RA, we hypothesise that the observed reduction in resistin levels may reflect the decreased number of synovial macrophages. Despite inducing low-grade inflammation, obesity is associated with reduced radiological damage, making adipocytokines, especially those related to obesity, likely regulators of this destructive process. We found that higher baseline resistin levels were associated with more radiological damage at baseline independent of inflammation. This is in accordance with two other cross-sectional studies. The role of resistin in the pathophysiology in the RA joint is supported by studies in mice showing that injection of resistin into the joint may induce arthritis associated with synovitis and pannus formation. Resistin has also been shown to have a role in osteoclast differentiation. We did not find an association between adiponectin levels and radiological damage. This is apparently in contrast with other studies showing an association between adiponectin levels and bone erosions. Of these studies two were prospective. The average adiponectin levels over time correlated better with bone erosions than the baseline levels, which may help to reconcile in part the discrepancy with our study. Moreover, radiological damage was scored at later time points (after respectively about 3 and 5 years than in our study). Consistent with our findings, most previous studies found no effect of TNF inhibition on circulating adiponectin levels in RA. Other studies have suggested an increase in adiponectin levels, in the absence of an effect on mRNA adiponectin levels in subcutaneous fat biopsies. Together, the effects of TNF inhibition on adiponectin levels are at present poorly understood. This study has some limitations. The number of patients in the GC cohorts is relatively small. In addition, there are differences in baseline characteristics like disease duration between the different cohorts. Of importance however, all patients had active RA and were treated according to a stringent treatment protocol. Adipocytokine levels were measured at different time points in the three cohorts after start of treatment. Therefore, it is too early to draw definitive conclusions with regard to the kinetics of the effects of different therapeutic interventions on various adipocytokines.
In conclusion, we found opposing effects of adalimumab and GC treatments on vaspin and visfatin serum levels, possibly in part explaining the different CVD risk profile of both drugs. Moreover, resistin levels are associated with radiological damage, independent of CRP levels or ACPA status. These data further support an important patho-physiological role for resistin and visfatin in RA.

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