EXTENDED REPORT

Treatment-specific changes in circulating adipocytokines: a comparison between tumour necrosis factor blockade and glucocorticoid treatment for rheumatoid arthritis

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INTRODUCTION
In rheumatoid arthritis (RA), synovitis may lead to progressive destruction of articular cartilage and subchondral bone. In addition, systemic inflammation, a hallmark of RA, is thought to play a key role in accelerated atherosclerosis, explaining the occurrence of accelerated atherosclerosis and CVD and are thought to play a role in the development of bone erosions.

ABSTRACT
Objective There is increasing evidence that adipocytokines may exert proinflammatory and destructive effects in rheumatoid arthritis (RA). Hence, the authors investigated the relationship between adipocytokines and several factors associated with RA (inflammation, joint destruction and cardiovascular disease), as well as the effect of treatment with a tumour necrosis factor inhibitor or glucocorticoids (GCs) hereupon.

Methods Serum levels of adiponectin, leptin, resistin, visfatin, vaspin and lipids were determined in a well-defined cohort of patients with RA before and after 16 weeks of adalimumab treatment (adalimumab cohort). The same parameters were analysed in two other cohorts of patients with RA 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 (CDBRA-GC cohort). Radiographs of hands and feet (adalimumab and CDBRA-GC cohorts) were assessed at baseline and after treatment.

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 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 anticitrullinated peptide antibodies status or C reactive protein levels.

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

RESULTS

The studies were performed according to the Declaration of Helsinki; all three cohorts were approved by the medical ethics committee, and all participants gave written informed consent.

PATIENTS AND METHODS
Patients from all cohorts fulfilled the 1987 American College of Rheumatology classification criteria for RA 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; 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 standardised 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 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.26

**High-dose GC 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;27 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-GC cohort**

Twenty-one patients were treated according to the 40-week, intensified COBRA trial as described earlier.28 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.29 Commercially available, quantitative sandwich ELISAs were used to determine serum levels of visfatin (Biovision, Mountain View, California, USA) and vaspin (AdipoGen, San Diego, California, 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 rheumatoid factor (RF), we preincubated all samples for the multiplex immunoassay with protein L (Pierce, Rockford, Illinois, USA), and residual immunoglobulins were blocked with equal volume of 10% (v/v) normal rat and mouse serum (Rockland, Gilbertsville, Pennsylvania, USA), as previously described.29 For the visfatin and visfatin ELISAs, three randomly selected samples of RF-negative patients with RA were spiked with freeze-dried RF (200 IU/ml) in a 1:1 or 1:3 ratio (SKML, Nijmegen, The Netherlands). Samples demonstrated high recovery across the concentration range, and we concluded that 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).30 No x-rays were available for the high-GC cohort.

**Statistical analysis**

Continuous data were described as mean (SD), if normally distributed, or median (IQR), if not normally distributed. The unpaired Student 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 χ² or Fisher’s exact test. Correlations were assessed with the Pearson product–moment or Spearman rank-order correlation coefficients. A paired Student t test or Wilcoxon signed rank test was used to determine significant changes from baseline within

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**Table 1** Baseline patient characteristics for EULAR good/moderate responders and non-responders after 16 weeks of adalimumab treatment

| Characteristics                  | All patients (n=48) | EULAR g/m (n=38) | EULAR non (n=10) | p Value |
|----------------------------------|---------------------|------------------|------------------|---------|
| Age (years)                      | 50 (13)             | 51 (13)          | 48 (17)          | 0.49    |
| Female, n (%)                    | 39 (81)             | 39 (81)          | 9 (90)           | 0.43    |
| DAS28                            | 5.5 (1.1)           | 5.6 (1.1)        | 5.0 (0.8)        | 0.11    |
| Erosive disease, n (%)           | 32 (67)             | 24 (63)          | 7 (70)           | 0.84    |
| RF n (%)                         | 31 (65)             | 28 (74)          | 5 (50)           | 0.82    |
| ACPO, n (%)                      | 33 (69)             | 27 (71)          | 6 (60)           | 0.50    |
| ESR (mm/h)                       | 20 (11–35)          | 20 (11–36)       | 19 (15–21)       | 0.72    |
| CRP (mg/dl)                      | 8 (6–19)            | 7 (4–20)         | 9 (6–21)         | 0.74    |
| Disease duration (months)        | 58 (31–143)         | 60 (28–143)      | 58 (26–201)      | 0.55    |
| MTX dose (mg/week)               | 19 (6.8)            | 19 (6.5)         | 19 (8.3)         | 0.85    |
| Concomitant oral GC, n (%)       | 13 (27)             | 8 (22)           | 4 (40)           | 0.18    |
| BMI                              | 27.0 (6.1)          | 27.4 (6.3)       | 24.4 (4.6)       | 0.17    |
| Resistin (ng/ml)                 | 24 (18–30)          | 23 (18–29)       | 26 (18–46)       | 0.48    |
| Adiponectin (mg/ml)              | 9.6 (7.14–14.0)     | 9.4 (7.4–12.7)   | 9.8 (8.4–17.9)   | 0.31    |
| Visfatin (mg/ml)                 | 0.46 (0.26–1.03)    | 0.42 (0.28–0.97) | 0.65 (0.26–1.34) | 0.51    |
| Resistin (ng/ml)                 | 2.6 (1.5–3.3)       | 2.5 (1.8–3.3)    | 2.6 (1.0–3.2)    | 0.49    |
| Leptin (ng/ml)                   | 57 (31–86)          | 57 (25–83)       | 59 (17–101)      | 0.95    |

Data are represented as mean (SD), median (IQR) or n (%), as appropriate. Baseline characteristics of patients with RA treated with adalimumab (40 mg subcutaneously every 2 weeks), in combination with a stable MTX dose for at least 16 weeks, are described. Patients were compared, based on clinical response—according to the EULAR response criteria—at 16 weeks resulting in good/moderate responders (g/m) and non-responders (non), with a χ² test, unpaired Student t test or Mann–Whitney U test, as appropriate. Presence of erosive joint disease was determined by x-ray. Presence of immunoglobulin M RF was defined as serum levels >12.5 IU/ml and presence of ACPO was defined as serum levels >25 IU/ml. ACPO, anticitrullinated peptide antibody; BMI, body mass index; CRP, C reactive protein; DAS28, disease activity score evaluated in 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GC, glucocorticoid; MTX, methotrexate; RF, IgM rheumatoid factor.
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Table 2  Baseline patient characteristics of GC and COBRA cohorts

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

Data are represented as mean (SD), median (IQR) or n (%), as appropriate. Baseline values of patients with RA treated with an oral GC (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), methotrexate (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. ACPA, anticitrullinated peptide antibody; CRP, C reactive protein; DAS28, disease activity score evaluated in 28 joints; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; RF, IgM rheumatoid factor.

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
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 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).

Pretreatment adipocytokine serum levels are not associated with DAS28

In the adalimumab cohort, serum levels of the different adipocytokines were not correlated with CRP, erythrocyte sedimentation rate (ESR) or DAS28 at baseline with the exception of adiponectin. Adiponectin was inversely associated with CRP ($r=-0.31$, $p=0.04$), ESR ($r=-0.33$, $p=0.02$) and DAS28 ($r=-0.26$, $p=0.08$) at baseline. 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 anticitrullinated peptide antibodies (ACPAs) and/or RF-positive patients with RA and age. In the high-GC cohort and the COBRA-GC cohort, adipocytokines...
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 GC 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 treatment compared with baseline (adiponectin: 72 (43–91) to 88 (62–122) ng/ml, $p=0.012$; leptin: 39 (13–120) to 53 (17–190) ng/ml, $p=0.025$; vaspin: 0.30 (0.22–0.64) to 1.01 (0.61–2.00) ng/ml, $p=0.008$; figure 2A). Visfatin 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) vaspin 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 showed any significant (gender and BMI adjusted) changes (figure 1C).

**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 profile. Visfatin levels at baseline were positively correlated to the TC/HDL (atherogenic index) and LDL/HDL ratios ($r=0.30$, $p=0.05$; $r=0.35$, $p=0.02$, respectively); 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 ratio ($r=0.31$, $p=0.04$) 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% CI 0.003 to 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 (adjusted $R^2=12\%$, $p=0.01$). A multiple regression analysis with resistin, ACPA status and disease duration as independent variables 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 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
cohort of patients with RA initiating antirheumatic treatment. TNF blockade or GC showed opposing effects on vispandin and visfatin serum levels: GC treatment (both short term and long term) increased vispandin, but not visfatin, while adalimumab led to decreased visfatin levels and had no effect on vispandin. 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 vispandin 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 vispandin level and decrease in vispandin concentrations, respectively. This latter relationship was independent of CRP levels, suggesting a role for vispandin specifically in the improvement of the lipid profile independent of a decrease in disease activity. Viscatin serum levels are also increased in patients with diabetes mellitus or hypertension and independently associated with increased CVD risk.32 The lipid profile improved after treatment with adalimumab and after treatment with GC in the COBRA-GC cohort. This effect has previously been ascribed to the decrease in inflammation after effective treatment.2

Another interesting finding in this study is the increase of vispandin levels in GC-treated patients, which were unaffected after adalimumab treatment. Increased vispandin levels are associated with decreased insulin sensitivity,33 34 which is commonly seen after GC treatment.36 Viscatin 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 patients with RA.36,37 We are the first to report altered resistin levels after long-term treatment with GC. As resistin is mainly produced by macrophages,8,38 and a decrease in the number of macrophages in synovium is consistently associated with improvement after effective treatment in RA,39,40 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,41,42 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.7,13 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.8 Resistin has also been shown to have a role in osteoclast differentiation.43 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.8,12 Of these studies, two were prospective.11,12 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 about 3 and 5 years, respectively) than in our study.11,12 Consistent with our findings, most previous studies found no effect of TNF inhibition on circulating adiponectin levels in RA.37,44 Other studies have suggested an increase in adiponectin levels,46,47 in the absence of an effect on mRNA adiponectin levels in subcutaneous fat biopsies.47 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 vispandin 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 pathophysiological role for resistin and visfatin in RA.

Contributors All authors meet the criteria for authorship and more specifically for contributorship statement: Berent Frakken and Wilco de Jager performed the adiponectin, resistin and leptin assays. Lilian van Tuyll and Mike Nurmmohamed supplied the databases of the COBRA-GC cohort. Danielle Gerlag collected and supplied the data of the high-GC cohort. Carla Wilbrands collected and supplied the data of the adalimumab cohort. Marieke Herenius and Ruth Klaasen performed the visfatin and vispandin assays. Ruth Klaasen and Marieke Herenius interpreted the data and wrote the article under the close supervision of Paul-Peter Tak and thereby take responsibility for this work. All other authors agreed to publish this work and critically reviewed the article. Conception and design of this work were discussed with all authors.

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Competing interests None.

Ethics approval This study was conducted with the approval of the medical ethical committees of the different universities.

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Data sharing statement Dear Dr Kien, I hereby would like to resubmit our manuscript entitled 'Treatment-specific changes in circulating adipocytokines: a comparison between tumour necrosis factor blockade and glucocorticoid treatment for rheumatoid arthritis' as an original contribution to Annals of the Rheumatic Diseases. We hope that you now find our article suitable for publication in Annals of the Rheumatic Diseases, on behalf of Professor Paul-Peter Tak, Ruth Klaasen.

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