High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis

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Abstract

Objective

To assess whether obesity and systemic inflammation are potential determinants of circulating adiponectin concentrations and whether low adiponectin levels cluster with metabolic syndrome features that are previously documented cardiovascular risk factors in rheumatoid arthritis (RA).

Methods

We investigated 33 RA patients who were treated with the TNF-α antagonist infliximab, immediately prior to an infliximab infusion. Adiponectin levels were also determined immediately after administration of an infliximab dose.

Results

Adiponectin concentrations correlated with age (R=0.465, p=0.008) and were higher in women (mean [95% confidence interval]=21 595 [15 366 to 30 349] ng/ml) than in men (9 310 [5 653 to 15 335] ng/ml)(p=0.008). C-reactive protein (CRP) levels correlated with circulating adiponectin concentrations (partial (p) R=-0.370, p=0.04), independent of age and gender. By contrast, the body mass index (BMI) did not correlate with adiponectin levels (pR=-0.039, p=0.8). Adiponectin concentrations correlated with triglycerides/HDL cholesterol ratios (pR=-0.396, p=0.03), total cholesterol/HDL cholesterol ratios (pR=-0.444, p=0.01) and high fasting plasma glucose levels (pR=-0.366, p=0.04), independent of CRP levels and the BMI. Adiponectin levels did not change (p=0.3) upon infliximab administration.

Conclusion

In this cohort, high-grade inflammation was independently and negatively correlated with circulating adiponectin concentrations whereas low adiponectin levels clustered with metabolic syndrome features that reportedly contribute to atherogenesis in RA. Circulating adiponectin may be involved in cardiovascular disease in RA. The impact of inflammation on circulating adiponectin concentrations is not likely to be TNF-α mediated in RA.

Key words

Circulating adiponectin, cardiovascular risk, rheumatoid arthritis.

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Conflict of interest:
Dr. Gonzalez-Gay attended a meeting in Miami on February 20th, 2008 to serve on the advisory board of Centocor and received less than $4000. However, the study was not supported by any pharmaceutical drug company. The other co-authors have declared no competing interests.

Introduction

In subjects without rheumatoid arthritis (RA), adipocytes and their surrounding macrophages produce a range of bioactive substances that are referred to as adipokines and that regulate systemic inflammation (1, 2), an increasingly recognized independent cardiovascular risk factor (3). The adipocyte-derived protein adiponectin is an especially promising candidate in explaining the link between obesity and systemic inflammation (1, 2). Indeed, low circulating adiponectin concentrations constitute a metabolic syndrome feature and circulating adiponectin has antiinflammatory, antiatherogenic and antidiabetic properties (1, 2, 4-10). Whether circulating adiponectin acts similarly in RA patients has not been determined.

The production and biological effects of adiponectin could be of particular importance in RA since this disease is characterized by high-grade inflammation (11, 12), an adverse fat distribution (13), and markedly increased cardiovascular event rates (11, 12, 14). Further, whereas adiponectin suppresses systemic inflammation in non-RA subjects, both TNF-α and interleukin (IL)-6 can also inhibit adiponectin production (1, 2, 15). TNF-α and IL-6 are produced in high quantities and play a pivotal role in RA (16, 17).

In healthy individuals, circulating adiponectin concentrations are negatively correlated with C-reactive protein levels (18). In RA, both an absent and positive correlation between circulating adiponectin and inflammation has been reported (19-21). Importantly, Schäffler *et al*. found that, in RA, human synovial fibroblasts produce adiponectin that enhances inflammation and matrix degeneration (23). Thus, inhibition of the production or biological effects of adiponectin deserves further investigation as a potential therapeutic strategy in inflammatory joint disease. It therefore appears important at this stage to determine whether *circulating* adiponectin could mediate other metabolic syndrome features that are known to increase the risk of cardiovascular disease in RA (25-27) since, if this is the case, adiponectin inhibition would be expected to be complicated by an increase in cardiovascular risk in this disease.

In the present study, we explored whether inflammation, obesity or both of these characteristics are potential determinants of circulating adiponectin concentrations, and whether low adiponectin concentrations cluster with metabolic syndrome features. Finally, we assessed adiponectin levels both before and after an infliximab infusion.

Material and methods

Patients

The 33 patients who participated in this study met the 1987 American College of Rheumatology criteria for RA (28) and form part of an ongoing study on cardiovascular disease in RA (27, 29-32). Each patient was on infliximab 3 or 5 mg/kg given at 6 or 8 weekly intervals (duration of therapy 1-4.5 years), oral methotrexate 15-25 mg weekly, prednisone 2.5-7.5 mg daily and a non-steroidal antiinflammatory agent (naproxen 500-1000 mg or diclofenac 50-100 mg daily). Twenty-eight (85%) patients were also on chloroquine 250 mg daily. Despite the use of infliximab, prednisone and methotrexate in each case, no patient experienced a disease remission (disease activity score (DAS)28 <2.4) (33) with the lowest recorded DAS28 being 3.4. Four patients were using a statin (simvastatin 20-40 mg daily). Patients with diabetes were excluded. The local institutional committee approved anti-TNF-α therapy and each patient gave informed consent to participate in the study.

Methods

The baseline recorded variables included demographic and RA characteristics, and metabolic syndrome features (Table I). Extraarticular RA manifestations were identified using the criteria as previously reported by Turesson *et al*. (34). Twenty-four extraarticular manifestations were identified in 16 (48%) patients. All measurements were made in the fasting state. Blood samples were taken at 0800 hours for the determination of the erythrocyte sedimentation rate, C-reactive protein (latex immunoturbidimetry), lipids (enzymatic colorimetry), plasma glucose, serum insulin

(DPC, Dipesa, Los Angeles, CA, USA) and total plasma adiponectin (ELISA, Linco Research, St. Charles, MO, USA; assay sensitivity = 0.5 ng/ml; intra-and interassay coefficients of variation = 3.3% and 5.5%, respectively), immediately prior to an infliximab infusion. The DAS 28 (35) was calculated and insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) (36). Hypertension was diagnosed in patients with a blood pressure of ≥140/90 mmHg and in those taking antihypertensive agents (enalapril (n=3); losartan (n=3); enalapril and hydrochlorothiazide (n=1). Subsequently, final blood sampling was performed for determination of adiponectin concentrations immediately after infliximab was administered over 120 minutes.

Data analysis

The data were analyzed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). Results are expressed as mean [95% confidence interval (CI)], geometric mean [95% CI] or number (n) (%). Non-normally distributed data were also logarithmically transformed prior to statistical analysis. Univariate relationships were assessed in simple linear regression models or by the Student's *t*-tests as appropriate. Relationships between baseline recorded characteristics and adiponectin were further evaluated using partial correlation analysis. The changes in adiponectin concentrations upon infliximab therapy were evaluated using the Student's *t*-test. Significance was set at 0.05.

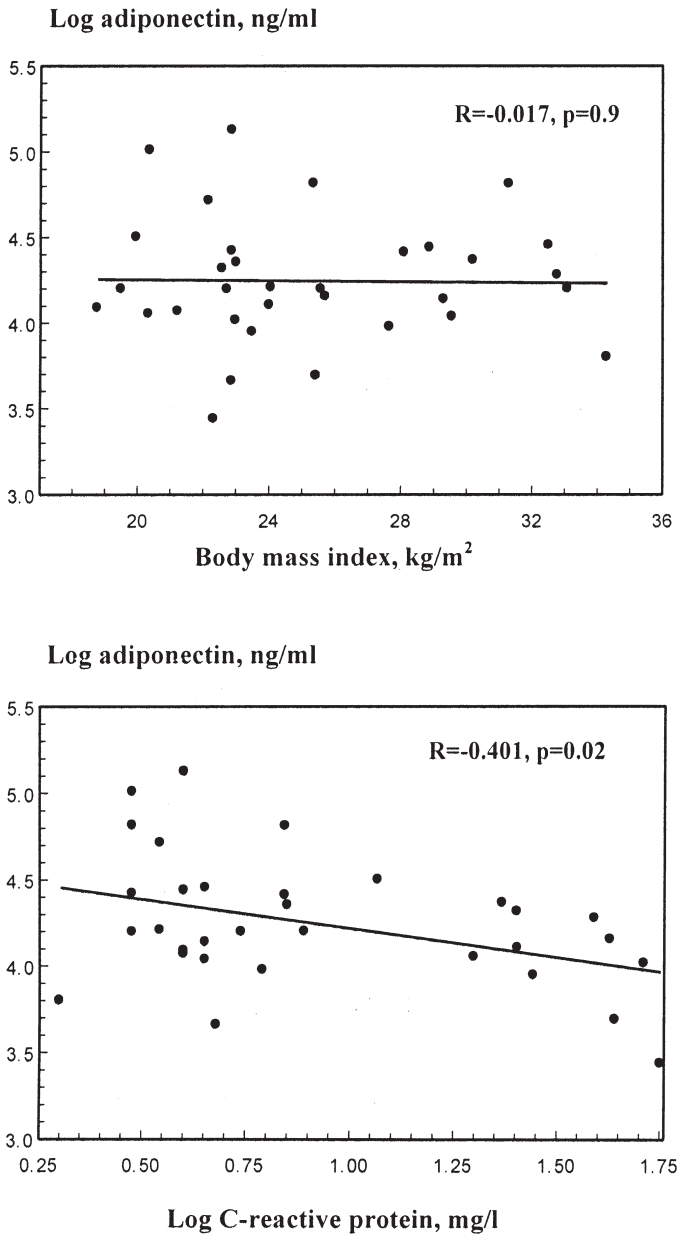


Fig. 1. The correlations of the body mass index and systemic inflammation with circulating adiponectin concentrations in univariate linear regression models.
Log: logarithmically transformed.

Results

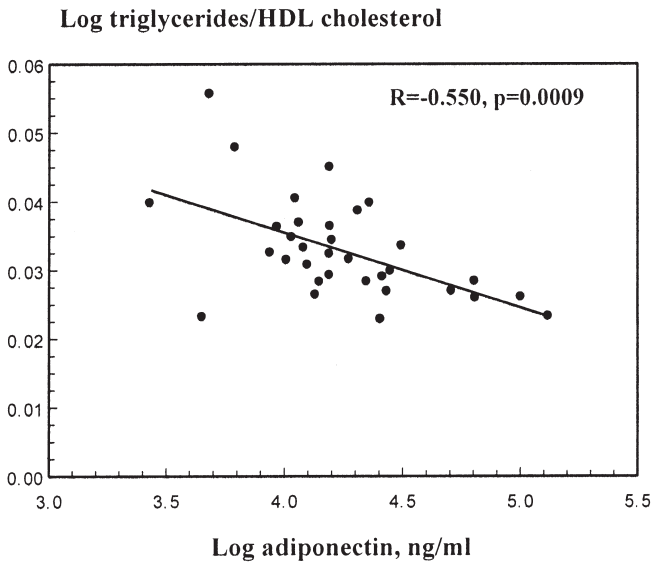
Relationships of demographic features, inflammation and adiposity with circulating adiponectin concentrations

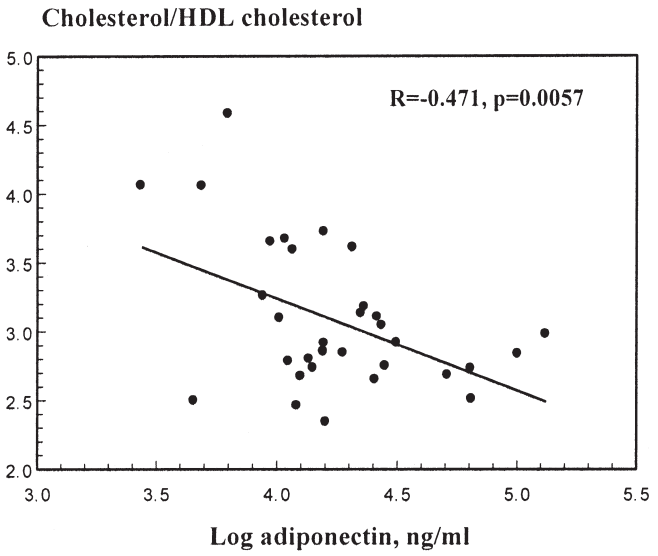
Adiponectin concentrations were correlated with age (R=0.465, p=0.008) and were higher in women (21 595 [15 366-30 349]) ng/ml) than in men (9 310 [5 653-15 335] ng/ml) (p=0.008).

As shown in Figure 1, the body mass index (BMI) did not correlate with adiponectin concentrations. By contrast, C-reactive protein levels were negatively correlated with adiponectin concentrations. After adjustment for the potentially confounding characteristics of age and gender, C-reactive protein concentrations remained correlated with circulating adiponectin levels (partial R=-0.370, p=0.04) whereas the correlation of the BMI with circulating adiponectin concentrations remained insignificant (partial R=-0.039, p=0.8). In the general population, adiposity is the main determinant of systemic inflammation whereas in RA, both RA disease activity and obesity reportedly contribute to circulating C-reactive protein concentrations (11, 37). In a separate partial correlation analysis (dependent variable was C-reactive protein and independent variables were the swollen joint count and the BMI), the swollen joint count contributed significantly to the variability in C-reactive protein concentrations (partial R^2=0.14, p=0.04) whereas the BMI did not correlate with C-reactive protein levels (partial R^2=0.01, p=0.5).

Relationships of adiponectin concentrations with metabolic syndrome features other than adiposity

Adiponectin concentrations were negatively correlated with the triglycerides/HDL cholesterol ratio, total cholesterol/HDL cholesterol ratio and plasma glucose levels as reflected in Figure





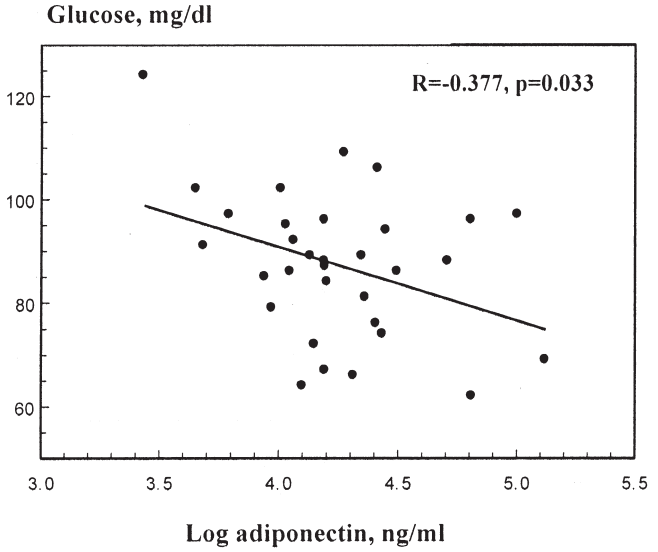


Fig. 2. Significant correlations of circulating adiponectin concentrations with metabolic syndrome features, other than obesity, in univariate linear regression models.
Log: logarithmically transformed.

2. Adiponectin concentrations were not significantly correlated with the HOMA-IR (R=-0.139, p=0.5), systolic (R=0.126, p=0.5) or diastolic blood pressure (R=0.079, p=0.7). Four patients were taking an angiotensin converting enzyme inhibitor and three an angiotensin II type 1 receptor blocker, agents that can increase adiponectin production (38). After adjustment for the use of these agents, the relationship between adiponectin concentrations and systolic and diastolic blood pressure remained non-significant ($p \geq 0.5$). Adiponectin concentrations were not significantly correlated with total cholesterol (R=0.209, p=0.3) and LDL cholesterol (R=-0.139, p=0.5).
Partial correlation coefficients [95% CI] of circulating adiponectin concentrations with the triglycerides/HDL cholesterol ratios, total cholesterol/HDL cholesterol ratios and plasma glucose levels, are shown in Figure 3. This revealed that the correlations of circulating adiponectin concentrations with atherogenic dyslipidemia and high plasma glucose were not explained by the potential determinants of impaired adiponectin production, *i.e.*, adiposity and systemic inflammation. The correlations of adiponectin concentrations with atherogenic dyslipidemia and high plasma glucose were also not affected after adjusting for the potential confounding variables of age, gender and the use of statin therapy (data not shown).

Relationships of adiponectin concentrations with other recorded baseline characteristics
Circulating adiponectin concentrations did not correlate with disease duration, the DAS28, swollen joint count, tender joint count, visual analog scale patient disease activity, erythrocyte sedimentation rate and cumulative prednisone dose, and were not associated with the presence of extraarticular manifestations and use of chloroquine ($p \geq 0.2$).

Changes in adiponectin concentrations upon infliximab therapy
Adiponectin concentrations (ng/ml) did not change (17 611 [13 020-23 820] before and 15 753 [11 712-21 188], p=0.3) after infliximab infusion)

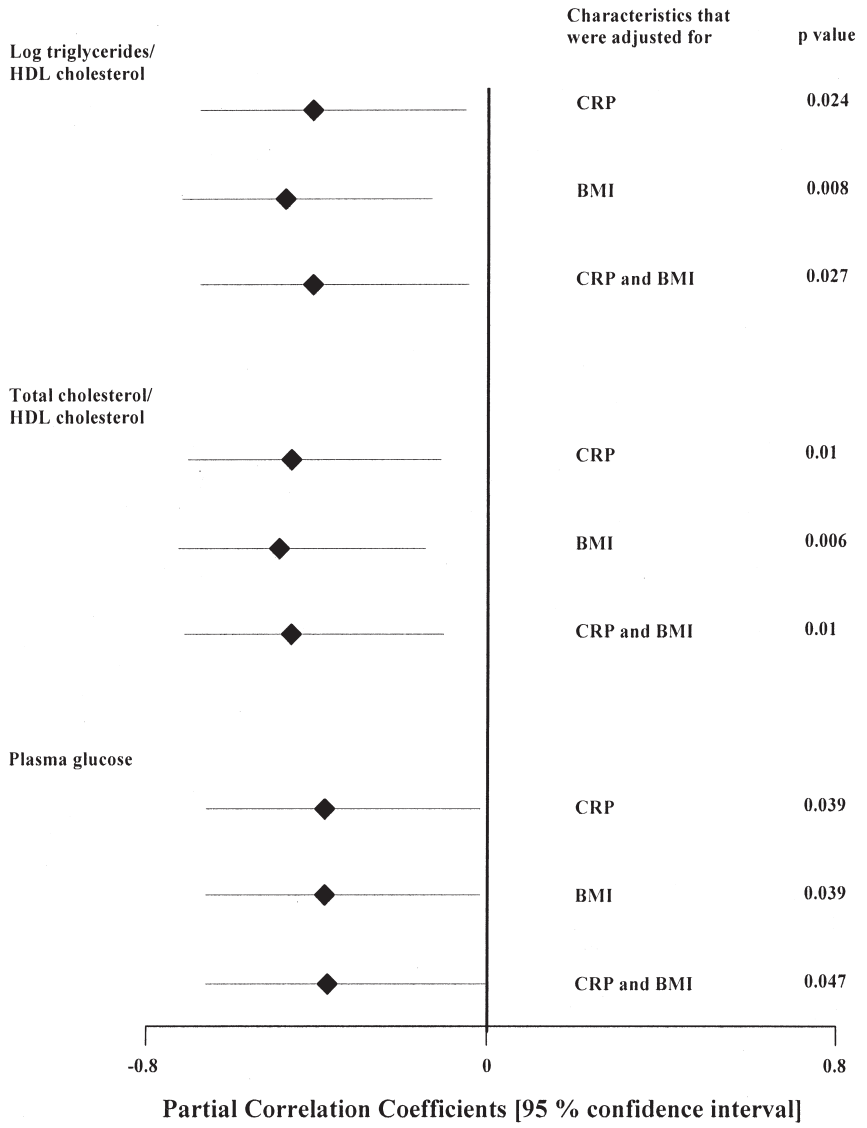


Fig. 3. The partial correlation coefficients for the relationships of circulating adiponectin concentrations with the metabolic syndrome features of atherogenic dyslipidemia and plasma glucose levels, after adjustment for covariates.
HDL: high density lipoprotein; CRP: C-reactive protein; BMI: body mass index.

and baseline adiponectin concentrations were strongly correlated with adiponectin levels after infliximab infusion (R=0.915, $p<0.0001$). The correlations of post infliximab circulating adiponectin concentrations with the baseline recorded characteristics (Table I) did not differ from the correlations of baseline circulating adiponectin concentrations with the baseline recorded characteristics (as described above) in both univariate and multivariable analysis (data not shown).

Discussion

In this cohort of patients with severe RA, C-reactive protein levels correlated independently with low circulating adiponectin concentrations. Systemic inflammation also correlates with decreased adiponectin production in non-RA subjects (1, 2, 18). Similar to the findings by Senolt *et al*., we also did not find a relationship between adiposity and circulating adiponectin concentrations in RA (20). By contrast, adiposity is reportedly strongly correlated with low adiponectin levels in non-RA subjects (1, 2, 10). This is attributable not only to metabolic dysfunction of enlarged fat cells in obesity but also to the production of excessive amounts of cytokines such as IL-6 and TNF-α by adipocytes and their surrounding macrophages that in turn inhibit adiponectin production (1, 2). In the present study, the swollen joint count explained a significant proportion of the variability in C-reactive protein concentrations whereas adiposity did not. Our results indicate that high-grade inflammation originating from the joints may be a stronger determinant of impaired adiponectin production than adiposity in RA.

In contrast to our findings and to what was previously found in non-RA subjects (1, 2, 18), both a lack of correlation (19, 20) and a positive correlation (21) between systemic inflammation and circulating adiponectin concentrations has been reported in RA. Our patients all had severe disease. Sixteen (49%) experienced extraarticular manifestations and each patient was treated with infliximab because of classical disease modifying agent refractory disease at the time of our study. Härle *et al*. found that current prednisone use was associated with lower adiponectin concentrations in RA (19). We could not assess the relationship of circulating adiponectin levels with current glucocorticoid use since each patient was employing this therapy. The cumulative glucocorticoid dose did not correlate with adiponectin levels in the present investigation. We considered previously documented pathophysiological interactions in our data analysis and interpretation of the results. However, as applies to previous studies on the relationship between circulating adiponectin concentrations and systemic inflammation in RA (19-21), our investigation was cross-sectionally designed and, therefore, the findings should be interpreted as hypothesis generating rather than definitive. Similarly, contrasting results were reported on the relationship of leptin production, another adipokine, with clinical or biological signs of disease activity in rheumatic disorders (39). Such discrepancies emphasize the need for future longitudinal studies in order to better define the interactions of adipokines with disease characteristics (39) and cardiovascular risk factors in these conditions.

Our most important finding comprised the clustering of low adiponectin concentrations with atherogenic dyslipidemia and high plasma glucose levels.

Table I. Baseline characteristics in 33 rheumatoid arthritis patients.

Demographic characteristics		
Age (years)	55	[51-60]
Women (n (%))	25	(76)
Disease duration (years)	12	[10-15]
Rheumatoid factor positive (n (%))	30	(91)
Disease activity		
DAS28	4.4	[4.0-4.7]
Swollen joint count	5	[3-6]
Tender joint count*	4	[3-5]
VAS patient disease activity	41	[35-47]
C-reactive protein (mg/l)*	8.3	[5.8-12.0]
Erythrocyte sedimentation rate (mm/hr)*	25	[19-31]
Extraarticular manifestations		
Any	16	(49)
Subcutaneous nodules	8	(24)
Secondary Sjögren's syndrome	8	(24)
Pulmonary fibrosis	3	(9)
Major cutaneous vasculitis	2	(6)
Vasculitis affecting other organs	2	(6)
Pleuritis	1	(3)
Metabolic syndrome features		
Body mass index (kg/m^2)	25.4	[23.8-26.9]
Glucose (mg/dl)	87	[82-92]
HOMA-IR (uU.mmol/ml.l)*	2.75	[2.14-3.47]
Triglycerides/HDL cholesterol*	1.08	[1.07-1.08]
Total cholesterol/HDL cholesterol	3.1	[2.9-3.3]
Systolic blood pressure (mmHg)	120	[116-134]
Diastolic blood pressure (mmHg)	73	[71-76]
Hypertension (n (%))	7	(21)
Total cholesterol (mg/dl)	192	[181-203]
LDL cholesterol (mg/dl)	104	[97-111]
Cumulative prednisone dose (gram)†	29.3	[23.3-36.0]
Chloroquine use	28	(85)

All measurements were made in the fasting state.
*Variables for which geometric means [95% confidence interval] are given.
†Calculated over entire duration of RA.
DAS: disease activity score; VAS: visual analog scale; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

This, again, is similar to the findings that were reported in studies on non-RA subjects (1, 2, 10). Yamauchi and colleagues recently provided a pathophysiological explanation for these relationships by showing that circulating adiponectin stimulates fatty acid oxidation in the liver and in skeletal muscle, increases glucose uptake in myocytes and reduces gluconeogenesis in hepatocytes (24). Each of these processes was mediated through activation of 5'adenosine monophosphate-activated protein kinase by circulating adiponectin (globular and full length adiponectin in skeletal muscle and only full length adiponectin in the liver) (24). We further found that the correlation of circulating adiponectin concentrations with atherogenic dyslipidemia and high plasma glucose levels was not explained by the potentially important determinants of decreased adiponectin production, *i.e.*, obesity and inflammation (1, 2, 15). It is of interest in this regard that in the Health Professionals Follow-up study, high adiponectin concentrations were found to reduce the risk of myocardial infarction independent of BMI, C-reactive protein and other classical cardiovascular risk factors (8). Whether low adiponectin concentrations contribute to the now well-recognized excess in cardiovascular disease in RA (11, 12, 14) deserves further study.

The potentially most important implication of our results is to be viewed in the context of the recent report by Ehling and colleagues (23). These investigators identified an enhancing effect on IL-6 and matrix metalloproteinase-1 production by adiponectin that originated from synovial fibroblasts in different arthritides. They further showed that TNF-α blockers reduced these effects of adiponectin. Although specific binding between TNF-α blockers and adiponectin could not be documented, the authors proposed that adiponectin may be a key target for therapeutic strategies in inflammatory joint diseases. Apart from the favorable effects of circulating adiponectin on lipid and glucose metabolism (1, 2, 24), this adipokine can also directly inhibit several important steps in atherogenesis (1, 2, 4-7). These findings together with our results suggest that, prior to the use of specific adiponectin inhibition in RA, the biological effects of circulating adiponectin concentrations on the vascular system requires further study in this disease. Further, selective intraarticular adiponectin inhibition that does not alter the biological effects of circulating adiponectin may need to be considered.

We found that infliximab did not alter circulating adiponectin concentrations. Similarly, Härle *et al.* found no effect of TNF-α blockade with adalimumab on circulating adiponectin concentrations (19). Although TNF-α can inhibit adiponectin production (1, 2), IL-6 constitutes another cytokine that may adversely affect adiponectin metabolism (15). This is relevant in the present context since, as previously discussed, we found that C-reactive protein was negatively correlated with adiponectin levels and IL-6 is an important determinant of C-reactive protein production by the liver (40). Future studies on adiponectin secretion should include measurement of proinflammatory molecules including different cytokines.

Finally, adiponectin levels correlated with age and were higher in women than in men. This is also in keeping with findings as reported in non-RA subjects (41-43). High adiponectin concentrations in the elderly and in women could translate into longevity and in the well-known gender-related later onset of cardiovascular disease in women, respectively (41, 42). Age and gender did not affect the relationships between

inflammation, adiponectin concentrations and metabolic syndrome features in our study.

We measured total adiponectin concentrations. Both low molecular weight- and higher molecular weight-adiponectin circulate in serum (44). Neumeier *et al*. recently showed that these different adiponectin isoforms exert both similar and different effects on monocytic cells (44). Thus, each isoforms induced apoptosis and activation of 5'adenosine monophosphate-activated protein kinase and reduced macrophage scavenger receptor A mRNA expression whereas only low molecular weight adiponectin displayed antiinflammatory properties (44). The interactions of different adiponectin isoforms with disease characteristics and cardiovascular risk factors in RA need to be addressed in future studies.

In conclusion, we found an independent negative correlation of high-grade inflammation with circulating adiponectin concentrations in this cohort of patients with severe RA. Low adiponectin concentrations further correlated independently with atherogenic dyslipidemia and high plasma glucose. These findings are similar to those previously reported in non-RA subjects and raise the possibility that low circulating adiponectin concentrations may be involved in cardiovascular disease in RA. However, the interaction of high-grade inflammation with low circulating adiponectin concentrations is not likely to be TNF-α mediated in this disease. The interactions between inflammation, adipokine metabolism and cardiovascular risk in RA require further evaluation in longitudinal studies.

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