Adiponectin and resistin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy

J.A. Miranda-Filloy[1], R. López-Mejias[2], F. Genre[2], B. Carnero-López[5], R. Ochoa[2], T. Diaz de Terán[3], C. González-Juanatey[6], R. Blanco[2], J. Llorca[4], M.A. González-Gay[2]

[1]Rheumatology Division, Hospital Xeral-Calde, Lugo, Spain; [2]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IFIMAV, Santander, Spain; [3]Department of Medicine, Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain; [4]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, IFIMAV, and CIBER Epidemiología y Salud Pública (CIBERESP), Santander, Spain; [5]Oncology Division, Hospital Del Bierzo, Ponferrada, León; [6]Cardiology Division, Hospital Xeral-Calde, Lugo, Spain.

Abstract

Objectives

The objective of this paper is to assess if disease activity, systemic inflammation and metabolic syndrome are potential determinants of circulating adiponectin and resistin levels in ankylosing spondylitis (AS) patients undergoing TNF-α antagonist therapy.

Methods

We investigated adiponectin and resistin serum concentrations in a series of 29 non-diabetic AS patients without history of cardiovascular (CV) events that were treated with the TNF-α antagonist infliximab, immediately prior to an infliximab infusion. Adipokine levels were also determined immediately after administration of an infliximab dose.

Results

A significant correlation between adiponectin concentrations and insulin sensitivity (QUICKI at the time of the study) was seen (r=0.384; p=0.05). Also, a marginally significant negative correlation between adiponectin serum levels and the body mass index was observed (r=-0.367; p=0.07). Circulating adiponectin and resistin concentrations did not correlate with disease duration, erythrocyte sedimentation rate, C-reactive protein, BASDAI or VAS at the time of the study. However, AS patients with hip involvement or synovitis and/or enthesitis in other peripheral joints had higher adiponectin concentrations than those who did not have these complications (p-value for both comparisons =0.01). Adiponectin and resistin levels did not change upon infliximab administration.

Conclusions

The present study shows that in non-diabetic patients with AS on treatment with infliximab adiponectin and resistin serum levels do not correlate with disease activity. Nevertheless, adiponectin concentration correlates with insulin sensitivity. This finding raises the possibility that low circulating adiponectin concentrations may be involved in the pathogenesis of the CV disease in AS.

Key words

ankylosing spondylitis, atherosclerosis, inflammation, anti-TNF-α antibody-infliximab, adiponectin, resistin

*José A. Miranda-Filloy, MD**
*Raquel López-Mejias, PhD**
Fernanda Genre, BSc
Rodrigo Ochoa, BSc
Ricardo Blanco, MD, PhD
Miguel A. González-Gay, MD, PhD
Teresa Diaz de Terán, MD
Javier Llorca, MD, PhD
Beatriz Carnero-López, MD
Carlos González-Juanatey, MD, PhD

**These authors made an equal contribution to this paper.*

Please address correspondence to:
Miguel A. González-Gay, MD, PhD,
Rheumatology Division,
Hospital Universitario Marqués de Valdecilla, IFIMAV,
Avenida de Valdecilla, s/n,
39008, Santander, Spain.
E-mail: miguelaggay@hotmail.com

Received on June 25, 2012; accepted in revised form on September 3, 2012.

Competing interests: none declared.

Introduction

Ankylosing spondylitis (AS) has been associated with a 1.5–2.0 increased mortality rate compared to that in the general population, which is mainly due to cardiovascular (CV) complications (1). Accelerated atherosclerotic disease seems to play the major role in the increased mortality observed in these patients (2). Several investigators disclosed increased common carotid artery intima-media wall thickness in patients with AS compared to controls, indicating early subclinical atherosclerosis associated with AS (3-5).

Besides chronic inflammation, classic CV risk factors such as obesity and its related metabolic syndrome are often present in patients with rheumatic diseases and have been proposed to influence the increased risk of CV disease observed in these patients. A systematic review confirmed that AS patients have higher risk of metabolic syndrome (6). In individuals with chronic inflammatory rheumatic diseases adipocytes and their surrounding macrophages produce a range of bioactive substances that are referred to as adipokines and that regulate systemic inflammation (7, 8). However, little is known about the function played by adiponectin and resistin, two adipose tissue derived factors, in atherosclerosis and AS. Adiponectin circulates in the blood in large amounts and it is secreted from adipocytes as different molecular forms (8). It increases fatty acid oxidation and reduces the synthesis of glucose in the liver and other tissues (8). Adiponectin exerts a protective function against CV disease and obesity. However, unlike observations in non-rheumatic patients, this adipokine acts as a proinflammatory factor in the inflamed joints promoting matrix degradation. Adiponectin levels have been found to be increased in patients with rheumatoid arthritis (RA) when compared with healthy controls (9). Nonetheless, results on adiponectin levels in AS have yielded contradictory results. In this regard, in a series of 53 AS patients with active disease serum adiponectin levels did not differ from those observed in controls (10). In contrast, in a series of 30 AS that started treatment with the anti-TNF-α-monoclonal antibody-infliximab, serum adiponectin levels obtained before the onset of infliximab therapy were significantly higher than in controls (11).

Resistin is another adipocyte-derived mediator that plays an important role in inflammation. Although resistin can be detected at very low levels in human adipose tissue, it is found in peripheral blood mononuclear cells (PBMC) (12), and resistin gene expression in PBMC is upregulated by proinflammatory cytokines such as TNF-α (13). Interestingly, high levels of resistin have been found in the synovial fluid from patients with RA (14). A positive correlation of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) with serum resistin has also been observed in RA patients (15-17). A recent report also disclosed significantly higher serum resistin levels in 30 AS patients compared with 30 controls (18).

As previously shown in RA (19), we have recently reported that non-diabetic patients with AS on treatment with infliximab, which specifically and with high affinity binds to TNF-α and neutralises this cytokine, experience a rapid and dramatic reduction in the serum insulin levels and a rapid improvement of insulin sensitivity following administration of this drug (20). Therefore, it is plausible to think that anti-TNF-α therapy might influence the mechanisms and mediators associated with the development of metabolic syndrome in AS.

Taken together all these considerations, in present study we explored whether inflammation, metabolic syndrome or both of these characteristics are potential determinants of circulating adiponectin concentrations, and if low adiponectin concentrations clustered with metabolic syndrome features in AS patients. We also assessed associations of circulating resistin concentrations with laboratory markers of inflammation and metabolic syndrome and demographic characteristics of these patients. Moreover, we investigated whether infliximab administration alters circulating adiponectin and resistin concentrations in a series of non-diabetic AS patients who required this therapy because of

disease refractory to non-steroidal anti-inflammatory drugs (NSAIDs).

Patients and methods

Patients

We assessed a series of 29 patients with AS attending hospital outpatient clinics seen over 14 months (January 2009 to March 2010), who fulfilled the modified New York diagnostic criteria for AS (21). They were treated by the same group of rheumatologists and were recruited from the Hospital Xeral-Calde, Lugo, Spain.

For ethical reasons, patients included in the present study were not randomised to a placebo group. The same procedure has been found acceptable and followed in studies on the short-term effect of infliximab therapy on the lipid profile in patients with RA (22).

Patients on treatment with infliximab seen during the period of recruitment with diabetes mellitus or with plasma glucose levels greater than 110 mg/dl were excluded. None of the patients included in the study had hyperthyroidism or renal insufficiency. Also, patients seen during the recruitment period who had experienced CV events, including ischaemic heart disease, heart failure, cerebrovascular accidents or peripheral arterial disease were excluded. Hypertension was diagnosed in patients with a blood pressure of ≥140/90 mmHg and in those taking antihypertensive agents. Obesity was defined if body mass index (BMI) – calculated as weight in kilograms divided by height in squared meters – was greater than 30.

In all cases anti-TNF-α monoclonal antibody-infliximab was prescribed because of active disease. All patients included in the current study had begun treatment with NSAIDs immediately after the disease diagnosis. All of them were still being treated with these drugs at the time of the study. At the time of this study most patients were on treatment with naproxen: 500–1000 mg/d. However, since the criterion for initiation of infliximab therapy was severe disease refractory to NSAIDs, all of them had been treated with at least 3 NSAIDs prior to the onset of infliximab therapy.

A clinical index of disease activity (Bath Ankylosing Spondylitis Disease Activity Index – BASDAI – range 0–10) (23) was evaluated in all patients at the time of the study. Clinical information on hip involvement, history of synovitis or enthesitis in other peripheral joints, history of anterior uveitis, presence of syndesmophytes and HLA-B27 status (typed by cell cytotoxicity) was assessed. Moreover, CRP – by a latex immunoturbidity method – ESR (Westergren), serum glucose, total cholesterol, HDL and LDL cholesterol and triglycerides (fasting overnight determinations) were assessed in all the patients at the time of the study. Also, information about CRP (by nephelometry) and ESR at the time of disease diagnosis was also reviewed.

Table I. Demographic, clinical and laboratory data of 29 patients with ankylosing spondylitis.

Variable	
Mean age (years) ±SD	
At the time of study	50.8 ± 15.0
At the time of onset of symptoms	28.3 ± 10.6
Delay to the diagnosis (years) ±SD	11.5 ± 9.2
Men/women	20/9
Mean disease duration (years) ±SD*	22.3 ± 13.3
History of classic cardiovascular risk factors	
Hypertension	12 (41.4%)
Dyslipidaemia	11 (37.9%)
Obesity (BMI >30 kg/m^2)	3 (10.3%)
Current smokers	12 (41.4%)
Mean blood pressure (mm Hg) ±SD*	
Systolic	124.0 ± 17.9
Diastolic	75.9 ± 12.7
Mean body mass index (kg/m^2) ±SD	26.7 ± 3.3
Mean BASDAI ±SD*	2.91 ± 2.13
Mean VAS ±SD*	31.2 ± 24.7
Hip involvement, n (%)	6 (20.7%)
Synovitis and/or enthesitis in other peripheral joints, n (%)	11 (37.9%)
Anterior uveitis, n (%)	5 (17.2%)
Syndesmophytes, n (%)	10 (34.5%)
Mean CRP (mg/l) ±SD**	
At the time of disease diagnosis	22.4 ± 32.8
At the time of study	6.4 ± 8.7
Mean ESR (mm/1st hour) ±SD***	
At the time of disease diagnosis	28.6 ± 27.5
At the time of study	19.6 ± 15.1
Mean cholesterol or triglycerides*	
Total cholesterol	198.9 ± 31.1
HDL cholesterol	53.0 ± 13.0
LDL cholesterol	126.5 ± 27.0
Triglycerides	95.1 ± 57.4
Mean fasting serum glucose (mg/dl) ±SD*	92.8 ± 8.8
HLA-B27 positive (n=26)	19 (73.1%)

*At the time of the study. **normal value <5 mg/l. ***normal value < 20 mm/1st hour.

The main demographic, clinical and laboratory data of this series of 29 AS patients at the time of the study are shown in Table I. Since at that time all patients were undergoing periodical treatment with the anti-TNF-α monoclonal antibody-infliximab, the mean BASDAI was only 2.91±2.13.

The local institutional committee approved anti-TNF-α therapy. Also, patients gave informed consent to participate in this study. Neither this study nor the former one on the short-term effect of infliximab therapy on insulin resistance in AS (20) was supported by any pharmaceutical drug company.

Study protocol

In all cases, the drug was given as an intravenous infusion in a saline solution over 120 minutes. All measurements were made in the fasting state. Blood samples were taken at 0800 hours for determination of the ESR (Westergren), CRP (latex immuno-turbidimetry), lipids (enzymatic colorimetry), plasma glucose and serum insu-

Table II. Partial correlation of serum resistin and adiponectin at time 0 with selected continuous variables adjusting by age at the time of the study, sex, and classic cardiovascular risk factors in 29 patients with ankylosing spondylitis.

Variable	r (with resistin)	*p*-value (with resistin)	r (with adiponectin)	*p*-value (with adiponectin)
Age at the onset of symptoms	-0.374	0.09	0.118	0.57
Disease duration*	0.373	0.09	-0.017	0.93
BMI*	-0.227	0.31	-0.367	0.07
Systolic blood pressure*	0.105	0.64	-0.108	0.60
Diastolic blood pressure*	-0.018	0.94	-0.111	0.59
BASDAI*	-0.101	0.65	-0.126	0.54
VAS*	-0.117	0.60	0.123	0.55
ESR* (natural-log-transformed)	0.254	0.25	-0.085	0.68
CRP* (natural-log-transformed)	0.043	0.85	-0.002	0.99
ESR** (natural-log-transformed)	0.235	0.29	-0.025	0.90
CRP** (natural-log-transformed)	0.259	0.24	-0.050	0.81
Total cholesterol* (natural-log-transformed)	0.061	0.79	0.094	0.65
HDL cholesterol*(natural-log-transformed)	-0.070	0.76	0.009	0.96
LDL cholesterol*(natural-log-transformed)	0.156	0.49	0.039	0.85
Triglycerides* (natural-log-transformed)	0.201	0.37	0.117	0.57
Serum glucose* (natural-log-transformed)	0.100	0.66	-0.177	0.39
HOMA-IR*	-0.326	0.14	-0.354	0.08
QUICKI*	0.393	0.07	0.384	0.05
Resistin at time 0			-0.054	0.81

*At the time of the study. **At the time of disease diagnosis.

lin (DPC, Dipesa, Los Angeles, CA, USA), total plasma adiponectin (ELISA, Linco Research, St. Charles, MO, USA; assay sensitivity=0.5 ng/ml; intra- and inter-assay coefficients of variation were 3.3% and 5.5%, respectively), and serum resistin (human resistin was measured by ELISA kit [Linco Research, St. Charles, MO, USA]; the assay sensitivity was 0.16 ng/ml and the intra- and inter-assay coefficients of variation were <5% and <7%, respectively) immediately prior to an infliximab infusion. As previously described, insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula = (insulin (μU/ml) x glucose (mmol/l) ÷ 22.5[7] (20). Subsequently, final blood sampling was performed for determination of adiponectin and resistin concentrations immediately after infliximab was administered over 120 minutes.

Statistical analyses

Correlation between basal adiponectin and resistin at time 0 with selected continuous variables was performed adjusting by age at the time of the study, sex, and classic cardiovascular risk factors via estimation of the Pearson partial correlation coefficient (r).

The associations between baseline characteristics and serum adiponectin and resistin concentrations were assessed by the Student's paired *t*-test for categorical variables. Differences in adiponectin and resistin levels between men and women and patients with hypertension or not were assessed by Mann-Whitney U-test.

Adiponectin and resistin serum levels before (time 0) and postinfusion (time 120) were compared using the paired Student *t*-test.

Two-sided *p*-values ≤0.05 were considered to indicate statistical significance. Analyses were performed using Stata 12/SE (StataCorp, College Station, TX, USA).

Results

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

Adiponectin and resistin concentrations did not show significant correlation with age at the onset of symptoms (Table II). Likewise, no differences in adiponectin or resistin concentrations between men and women were observed (Table III). Also, no correlation between CRP and ESR at the time of the study or at the time of disease diagnosis and adiponectin and resistin concentrations were seen. Nevertheless, a marginally significant correlation between adiponectin serum levels and BMI was observed (r=-0.367; *p*= 0.07) (Table II).

Relationships of adiponectin and resistin concentrations with metabolic syndrome features other than adiposity

No significant correlation between adiponectin and resistin concentrations with systolic or diastolic blood pressure, total cholesterol, HDL and LDL-cholesterol, triglycerides and glucose levels were observed (Table II). In keeping with these observations, no significant differences in adiponectin and resistin concentrations were seen when patients were stratified according to the presence or absence of hypertension and dyslipidaemia (Table III). Nevertheless, a significant correlation between adiponectin concentrations and insulin sensitivity (QUICKI at the time of the study) was found (r=0.384; *p*=0.05) (Table II).

Relationships of adiponectin and resistin concentrations with other recorded baseline characteristics

Circulating adiponectin and resistin concentrations did not correlate with disease duration, BASDAI and VAS at the time of the study (Table II). Likewise, no differences in adiponectin and resistin concentrations were observed when patients with a history of anterior uveitis or presence of syndesmophytes were compared with the remaining patients who did not exhibit these features (Table III). It was also the case when patients were compared according to HLA-B27 status (Table III). Nevertheless, patients with hip involvement or synovitis and/or enthesitis in other peripheral joints had higher adiponectin concentrations than those who did not have these complications (*p*-value for both comparisons =0.01) (Table III).

Changes in adiponectin and resistin concentrations upon infliximab therapy

Adiponectin and resistin concentrations did not change before and after infliximab infusion (Table IV), and baseline adiponectin concentrations were not

Table III. Differences in basal resistin and adiponectin (time 0) according to categorical variables.

Variable	Category	Resistin mean±SD	*p*-value mean±SD	Adiponectin	*p*-value
Sex	Men	14.63 ± 7.90	0.79	15013 ± 6705	0.46
	Women	15.47 ± 6.77		17256 ± 9017	
Arterial hypertension	Yes	13.45 ± 7.40	0.32	16621 ± 6042	0.59
	No	16.36 ± 6.71		15066 ± 8356	
Dyslipidaemia	Yes	11.69 ± 5.58	0.09	17421 ± 7330	0.34
	No	16.85 ± 7.13		14664 ± 7462	
Obesity	Yes	10.91 ± 3.36	0.38	14205 ± 8801	0.72
	No	15.57 ± 7.15		15883 ± 7412	
Current smoker	Yes	16.91 ± 6.63	0.33	12960 ± 5903	0.09
	No	14.06 ± 7.22		17650 ± 7897	
Hip involvement	Yes	15.14 ± 4.96	0.98	22418 ± 5086	0.01
	No	15.22 ± 7.65		13959 ± 6961	
Synovitis and/or enthesitis in other peripheral joints	Yes	15.52 ± 7.28	0.84	20003 ± 6751	0.01
	No	14.95 ± 7.04		13086 ± 6657	
Anterior uveitis	Yes	10.57 ± 5.45	0.10	18480 ± 7312	0.37
	No	16.36 ± 6.97		15132 ± 8057	
Syndesmophytes	Yes	15.69 ± 8.15	0.78	16669 ± 5455	0.62
	No	14.87 ± 6.40		15205 ± 8347	
HLA-B27	Positive	14.49 ± 7.24	0.47	15343 ± 7543	0.72
	Negative	16.71 ± 6.64		14107 ± 7641	

Table IV. Differences between basal (time 0) and postinfusion (time 120 minutes) resistin and adiponectin serum concentration.

	Basal (time 0)	Postinfusion (time120)	*p*-value
Resistin			
Mean±SD (ng/ml)	15.20 ± 7.00	14.61 ± 7.16	0.63
(Median; IQ range)	14.58 (9.37–18.07)	14.19 (9.52–17.85)	
Adiponectin			
Mean±SD (ng/ml)	15709 ± 7406	14845 ± 6280	0.19
(Median; IQ range)	14117 (10428–22285)	13672 (10392–19674)	

correlated with resistin levels obtained immediately before infliximab infusion (Table II).

Correlations of post infliximab circulating adiponectin and resistin concentrations with the baseline recorded characteristics did not differ from the correlations of baseline circulating adiponectin and resistin concentrations (obtained at time 0) with the baseline recorded characteristics (data not shown).

Discussion

Anti-TNF-α therapy has been found to be effective in patients with AS and other spondyloarthropathies (24-26). This fact may explain the low disease activity observed at the time of the study in this series of AS undergoing infliximab therapy.

Adipokines such as adiponectin and resistin are involved in the regulation of inflammation (27). Adiponectin controls insulin sensitivity, endothelial function, and immunity. Yet, information on this adipokine in patients with AS is limited (10, 11). Although systemic inflammation was found to correlate negatively with adiponectin levels in obese and RA subjects (8, 28, 29), in our cohort of AS patients undergoing periodical anti-TNF-α therapy, CRP and ESR levels did not correlate with low circulating adiponectin concentrations. This lack of correlation between inflammation and adiponectin serum levels in AS was also found by Toussirot *et al*. (10).

In our series of anti-TNF-α treated AS patients, we observed a marginally significant negative correlation between adiponectin serum levels and BMI. Adiposity was also reported to correlate with low adiponectin levels in non-RA subjects (7, 8). This was 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 (7, 8). However, unlike RA patients with severe disease in whom high-grade inflammation originating from the joints may be a stronger determinant of impaired adiponectin production than adiposity (29), our results indicate that in AS patients undergoing anti-TNF-α therapy adiposity may be a stronger determinant of a reduced adiponectin production than the low-grade inflammation found in these patients.

AS is part of a bigger family of seronegative spondylarthrotpathies, which encompasses also psoriatic arthritis and inflammatory bowel disease. Common pathogenic pathways are likely to be shared by these diseases. In this regard, subclinical atherosclerosis and increased incidence of CV mortality has been observed in patients with psoriatic arthritis (30-32). In line with this, previous studies investigated adiponectin and resistin in psoriatic arthritis or inflammatory bowel disease patients. In keeping with our results on AS and RA (29), Peters *et al*. did not observe a significant change in adiponectin levels over time with anti-TNF-α therapy in patients with psoriatic arthritis (33). Nevertheless, as observed in patients with AS (18), patients with inflammatory bowel disease had higher resistin levels than controls (34). Also, resistin levels were found to be an independent predictor of disease activity in patients with Crohn's disease (34).

Different mechanisms including insulin resistance contribute to the development of endothelial dysfunction that is an early step in the atherogenesis process. In our study, we observed a significant correlation between adiponectin concentrations and insulin sensitivity. This beneficial effect of adiponectin on insulin sensitivity is mediated in part by its ability to activate 5'adenosine monophosphate-activated protein kinase (AmPK) in skeletal muscle and liver, because AmPK activation leads to an increase in fatty acid oxidation and glucose uptake in muscle tissue, and inhibition of gluconeogenesis in the liver (35). It may be of potential in-

terest 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 CRP and classical CV risk factors (36). However, unlike RA patients with severe disease (29), in our series of AS patients that at the time of study had low levels of inflammation, we did not observe correlation between low concentration of adiponectin and dyslipidaemia.

Previous studies showed no clear correlations between serum concentrations of adiponectin and disease activity in RA patients undergoing anti-TNF-α therapy (37). In keeping with these observations, our data and those from another series (10) showed no correlation between BASDAI and adiponectin levels in AS.

Paradoxically, in contrast to the protective effect on CV disease, adiponectin acts as a pro-inflammatory factor in joints and it could be involved in matrix degradation. Adiponectin levels have been found to be higher in RA patients than in healthy controls (9). Adiponectin and adiponectin receptor 1 expression is higher in synovial fluids and the synovial tissues of RA patients compared with controls, confirming the correlation of circulating adiponectin levels with the severity of RA (38). In keeping with these observations, we observed that AS patients with hip involvement and those with synovitis and/or enthesitis in other peripheral joints exhibited higher adiponectin levels than the remaining AS patients without clinically evident peripheral involvement. Therefore, higher adiponectin levels might help to establish a subgroup of AS patients with predominant peripheral involvement.

Contradictory results regarding differences in serum resistin levels between patients with rheumatic diseases and controls have been reported. Some studies revealed higher resistin concentration in RA patients, while others did not disclose differences with controls (9, 15, 39). A recent study has showed higher serum resistin levels in 30 patients with AS compared to 30 healthy subjects (18). Yet, information on resistin in AS is limited and it is especially true when we specifically focused on resistin levels in AS patients undergoing anti-TNF-α therapy. In this regard, unlike patients with severe RA in whom serum resistin levels correlated with CRP and disease activity, thus suggesting a role of this adipokine in the pathogenesis of RA (17), no correlation between resistin concentration and ESR, CRP, or BASDAI was observed by Kocabas *et al*. in a series of 30 AS patients (18). In keeping with these findings, we did not observe correlation between resistin concentration and disease activity and laboratory markers of inflammation in our series of AS treated with the TNF-α antagonist-infliximab. Thus, these differences with respect to RA need to be clarified. A potential explanation may be the lower inflammatory burden in AS, in particular in anti-TNF-α treated patients, compared with individuals diagnosed with RA and severe disease.

Regarding the potential effect that anti-TNF-α therapy could make on adipokine concentrations, we found that infliximab infusion did not alter circulating adiponectin concentrations in AS patients. Similarly, Popa *et al*. found no short or long-term effect of TNF-α blockade on circulating adiponectin concentrations in RA (37). Similarly, in contrast to results observed in patients with severe RA in whom anti-TNF-α therapy resulted in a rapid reduction of serum resistin levels, infliximab infusion did not lead to significant reduction in resistin serum levels in our cohort of AS patients. Distinct pathogenic mechanisms leading to different degree of severity of the inflammatory burden might explain the differences between RA and AS.

Potential limitations in our study may exist. With respect to this, we measured total adiponectin concentrations. Both low molecular weight- and higher molecular weight-adiponectin circulate in serum (40). Neumeier *et al*. described that these different adiponectin isoforms exerted both similar and different effects on monocytic cells (40). Therefore, each isoform 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 (40). The interactions of different adiponectin isoforms with disease characteristics and CV risk factors in AS need to be addressed in future studies. Another potential limitation was that our investigation was cross-sectionally designed and, therefore, the findings should be interpreted as hypothesis-generating rather than definitive. Therefore, future longitudinal studies in order to better define the interactions of adipokines with disease characteristics and CV risk factors in AS are required.

Conclusion

In conclusion, the present study indicates that in non-diabetic patients with AS on treatment with infliximab adiponectin and resistin serum levels do not correlate with disease activity. Nevertheless, adiponectin concentration correlates with insulin sensitivity. This finding is similar to that previously reported in non-AS subjects and raises the possibility that low circulating adiponectin concentrations may be involved in the pathogenesis of the CV disease in AS. However, further studies are needed to elucidate the implication of inflammation and adipokines in the CV risk of patients with AS.

Acknowledgements

The authors thank Mrs Susana Escandon and Isabel Castro-Fernandez, nurses from the Rheumatology Outpatient Clinic, Ms Pilar Ruiz, a nurse from the Haematology Division, and the members of the Biochemistry Department from Hospital Xeral-Calde, Lugo, for their valuable help in undertaking this study.

References

1. PETERS MJ, VAN DER HORST-BRUINSMA IE, DIJKMANS BA, NURMOHAMED MT: Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. *Semin Arthritis Rheum* 2004; 34: 585-92.
2. PETERS MJ, VISMAN I, NIELEN MM *et al*.: Ankylosing spondylitis: a risk factor for myocardial infarction? *Ann Rheum Dis* 2010; 69: 579-81.
3. GONZALEZ-JUANATEY C, VAZQUEZ-RODRIGUEZ TR, MIRANDA-FILLOY JA *et al*.: The high prevalence of subclinical atherosclerosis

in patients with ankylosing spondylitis without clinically evident cardiovascular disease. *Medicine* (Baltimore) 2009; 88: 358-65.
4. PETERS MJ, VAN EIJK IC, SMULDERS YM *et al*.: Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. *J Rheumatol* 2010; 37: 161-6.
5. BODNÁR N, KEREKES G, SERES I *et al*.: Assessment of subclinical vascular disease associated with ankylosing spondylitis. *J Rheumatol* 2011; 38: 723-9.
6. MATHIEU S, GOSSEC L, DOUGADOS M, SOUBRIER M: Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis. *Arthritis Care Res* (Hoboken) 2011; 63: 557-63.
7. BERG AH, SCHERER PE: Adipose tissue, inflammation, and cardiovascular disease. *Circ Res* 2005; 96: 939-49.
8. OH DK, CIARALDI T, HENRY RR: Adiponectin in health and disease. *Diabetes Obes Metab* 2007; 9: 282-9.
9. OTERO M, LAGO R, GOMEZ R *et al*.: Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 1198-201.
10. TOUSSIROT E, STREIT G, NGUYEN NU *et al*.: Adipose tissue, serum adipokines, and ghrelin in patients with ankylosing spondylitis. *Metabolism* 2007; 56: 1383-9.
11. DERDEMEZIS CS, FILIPPATOS TD, VOULGARI PV, TSELEPIS AD, DROSOS AA, KIORTSIS DN: Leptin and adiponectin levels in patients with ankylosing spondylitis. The effect of infliximab treatment. *Clin Exp Rheumatol* 2010; 28: 880-3.
12. PATEL L, BUCKELS AC, KINGHORN IJ *et al*.: Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. *Biochem Biophys Res Commun* 2003; 300: 472-6.
13. KASER S, KASER A, SANDHOFER A, EBENBICHLER CF, TILG H, PATSCH JR: Resistin messenger-RNA expression is increased by proinflammatory cytokines *in vitro*. *Biochem Biophys Res Commun* 2003; 309: 286-90.
14. SCHÄFFLER A, EHLING A, NEUMANN E *et al*.: Adipocytokines in synovial fluid. *JAMA* 2003; 290: 1709-10.
15. MIGITA K, MAEDA Y, MIYASHITA T *et al*.: The serum levels of resistin in rheumatoid arthritis patients. *Clin Exp Rheumatol* 2006; 24: 698-701.
16. SENOLT L, HOUSA D, VERNEROVA Z *et al*.: Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis* 2007; 66: 458-63.
17. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, GONZALEZ-JUANATEY C *et al*.: Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 311-6.
18. KOCABAS H, KOCABAS V, BUYUKBAS S, MELIKOGLU MA, SEZER I, BUTUN B: The serum levels of resistin in ankylosing spondylitis patients: a pilot study. *Rheumatol Int* 2012; 32: 699-702.
19. GONZALEZ-GAY MA, DE MATIAS JM, GONZALEZ-JUANATEY C *et al*.: Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24: 83-6.
20. MIRANDA-FILLOY JA, LLORCA J, CARNERO-LÓPEZ B, GONZÁLEZ-JUANATEY C, BLANCO R, GONZÁLEZ-GAY MA: TNF-α antagonist therapy improves insulin sensitivity in non-diabetic ankylosing spondylitis patients. *Clin Exp Rheumatol* 2012 [Epub July 5].
21. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
22. VIS M, NURMOHAMED MT, WOLBINK G *et al*.: Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32: 252-5.
23. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91
24. D'ANGELO S, PALAZZI C, CANTINI F *et al*.: Etanercept in spondyloarthopathies. Part II: Safety and pharmacoeconomic issues. *Clin Exp Rheumatol* 2011; 29: 865-70.
25. PALAZZI C, D'ANGELO S, CANTINI F *et al*.: Etanercept in spondyloarthropathies. Part I: Current evidence of efficacy. *Clin Exp Rheumatol* 2011; 29: 858-64.
26. HELDMANN F, BRANDT J, VAN DER HORST-BRUINSMA IE *et al*.: The European ankylosing spondylitis infliximab cohort (EASIC): a European multicentre study of long term outcomes in patients with ankylosing spondylitis treated with infliximab. *Clin Exp Rheumatol* 2011; 29:672-80.
27. GÓMEZ R, CONDE J, SCOTECE M, GÓMEZ-REINO JJ, LAGO F, GUALILLO O: What's new in our understanding of the role of adipokines in rheumatic diseases? *Nat Rev Rheumatol* 2011; 7: 528-36.
28. ROLLAND YM, PERRY HM, PATRICK P, BANKS WA, MORLEY JE: Leptin and adiponectin levels in middle-aged postmenopausal women: associations with lifestyle habits, hormones, and inflammatory markers – a cross-sectional study. *Metabolism* 2006; 55: 1630-6.
29. GONZALEZ-GAY MA, LLORCA J, GARCIA-UNZUETA MT *et al*.: High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 596-603.
30. GONZALEZ-JUANATEY C, LLORCA J, MIRANDA-FILLOY JA *et al*.: Endothelial dysfunction in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 2007; 57: 287-93.
31. GONZALEZ-JUANATEY C, LLORCA J, AMIGO-DIAZ E, DIERSSEN T, MARTIN J, GONZALEZ-GAY MA: High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 2007; 57: 1074-80.
32. GLADMAN DD, ANG M, SU L, TOM BD, SCHENTAG CT, FAREWELL VT: Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis* 2009; 68: 1131-5.
33. PETERS MJ, WATT P, CHERRY L *et al*.: Lack of effect of TNFalpha blockade therapy on circulating adiponectin levels in patients with autoimmune disease: results from two independent prospective studies. *Ann Rheum Dis* 2010; 69: 1687-90.
34. KONRAD A, LEHRKE M, SCHACHINGER V *et al*.: Resistin is an inflammatory marker of inflammatory bowel disease in humans. *Eur J Gastroenterol Hepatol* 2007; 19: 1070-4.
35. YAMAUCHI T, KAMON J, MINOKOSHI Y *et al*.: Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002; 8: 1288-97.
36. PISCHON T, GIRMAN CJ, HOTAMISLIGIL GS, RIFAI N, HU FB, RIMM EB: Plasma adiponectin levels and risk of myocardial infarction in men. *J Am Med Assoc* 2004; 291: 1730-7.
37. POPA C, NETEA MG, DE GRAAF J *et al*.: Circulating leptin and adiponectin concentrations during tumor necrosis factor blockade in patients with active rheumatoid arthritis. *J Rheumatol* 2009; 36: 724-30.
38. TAN W, WANG F, ZHANG M, GUO D, ZHANG Q, HE S: High adiponectin and adiponectin receptor 1 expression in synovial fluids and synovial tissues of patients with rheumatoid arthritis. *Semin Arthritis Rheum* 2009; 38: 420-7.
39. BOKAREWA M, NAGAEV I, DAHLBERG L, SMITH U, TARKOWSKI A: Resistin, an adipokine with potent proinflammatory properties. *J Immunol* 2005; 174: 5789-95.
40. NEUMEIER M, WEIGERT J, SCHÄFFLER A *et al*.: Different effects of adiponectin isoforms in human monocytic cells. *J Leukoc Biol* 2006; 79: 803-8.