Leptin and visfatin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy

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Abstract

Objectives

This paper aims to determine whether disease activity, systemic inflammation and metabolic syndrome are potential determinants of circulating leptin and visfatin levels in ankylosing spondylitis (AS) patients undergoing TNF-α antagonist therapy. We also assessed whether the infusion of infliximab may alter circulating leptin and visfatin concentrations in these patients.

Methods

We investigated leptin and visfatin serum concentrations in a series of 30 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. Leptin and visfatin levels were also determined immediately after administration of an infliximab dose.

Results

Significant differences in leptin concentrations between men (8.85±5.31 ng/ml) and women (18.96±9.72 ng/ml) were observed (p=0.001). A significant correlation between visfatin concentrations and insulin resistance (HOMA at the time of the study) was found (r= 0.493; p=0.009). Circulating leptin and visfatin concentrations did not correlate with disease duration, erythrocyte sedimentation rate, C-reactive protein, BASDAI and VAS at the time of the study and adiponectin and resistin levels prior to infliximab infusion. Likewise, no differences in leptin and visfatin 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. Leptin and visfatin levels did not change upon infliximab administration.

Conclusion

The present study indicates that in non-diabetic patients with AS on treatment with infliximab leptin and visfatin serum levels do not correlate with disease activity or systemic inflammation. Nevertheless, visfatin concentration correlates with insulin resistance.

Key words

ankylosing spondylitis, atherosclerosis, inflammation, anti-TNF-α antibody-infliximab, leptin, visfatin

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Introduction

Cardiovascular (CV) disease is the leading cause of mortality in patients with ankylosing spondylitis (AS) (1, 2). Surrogate markers of CV disease supports the claim of accelerated atherosclerosis in patients with AS when compared with controls (3-5).

Besides chronic inflammation, AS patients have higher risk of metabolic syndrome (6). In individuals with chronic inflammatory rheumatic diseases, adipocytes and their surrounding macrophages produce a range adipokines that are bioactive substances implicated in the regulation of the systemic inflammation (7). However, information on leptin and visfatin in AS patients, in particular in those undergoing anti-tumour necrosis factor (TNF)-α therapy, and their potential implication in the mechanisms leading to accelerated atherosclerosis in AS is limited.

Leptin plays an important role in the regulation of body weight by inhibiting food intake and stimulating energy expenditure (8). It is also a proinflammatory adipocyte-derived factor that operates in the cytokine network by linking immune and inflammatory processes to the neuroendocrine system (8, 9). Leptin regulates and participates both in immune homeostasis and in inflammatory processes and seems to be implicated in the complex mechanism associated with some autoimmune diseases such as rheumatoid arthritis (RA) (10). Leptin levels are mostly dependent on the amount of body fat, but its synthesis is also regulated by inflammatory mediators such as TNF-α and interleukin (IL)-1 (10).

The levels of this adipokine have been found to be increased in patients with RA when compared with healthy controls (11). However, results on leptin levels in AS have yielded contradictory results. Park *et al*. reported that leptin production was increased in 20 patients with active AS compared with 20 controls (12). However, in a series of 53 AS patients with active disease, circulating levels of leptin were lower than in 35 controls, even after adjustment for fat mass (13). In keeping with these findings, in another series, leptin levels were significantly lower in 28 AS patients than in 17 healthy controls (14). In contrast, in a series of 30 AS patients that started treatment with the anti-TNF-α-monoclonal antibody-infliximab, serum leptin levels obtained before the onset of infliximab therapy were similar to those found in controls (15). Moreover, serum levels of leptin did not change significantly after a 6-month infliximab treatment programme (15).

Visfatin, also known as pre-B cell colony-enhancing factor or PBEF, is an insulin-mimetic adipokine (16) that has also been associated with inflammation (17-20). Circulating levels of visfatin were found to correlate with the amount of visceral fat (21). Recombinant visfatin activates human leukocytes and induces the production of IL-1β, TNF-α, and IL-6 (19). Otero *et al*. disclosed higher circulating visfatin levels in patients with RA compared to healthy subjects (11). Brentano *et al*. confirmed the role of visfatin as a proinflammatory and matrix-degrading mediator of joint inflammation in RA (18). In a series of 26 AS patients with mild to moderate disease, no correlation was found between visfatin levels and disease activity, functional status or acute-phase-reactants (22). In this series of AS patients, a 3-month intensive physiotherapy programme led to clinical improvement that was not associated with a significant change in the serum levels of visfatin (22).

As reported in RA (23), the administration of a single infusion of infliximab yielded a rapid and dramatic reduction in the serum insulin levels and a rapid improvement of insulin sensitivity in AS patients (24). Therefore, we are tempted to hypothesise that anti-TNF-α therapy might influence the mechanisms and mediators associated with the development of metabolic syndrome in AS. With respect to this, we observed that in non-diabetic patients with AS on treatment with infliximab adiponectin and resistin serum levels did not correlate with disease activity (25). Nevertheless, adiponectin concentration correlated with insulin sensitivity (25).

In line with the above, in the present study we investigated whether inflammation, adiposity, insulin resistance or some other characteristics associated

with the development of metabolic syndrome are potential determinants of circulating leptin and visfatin concentrations in a series non-diabetic AS patients on periodical treatment with the TNF-α-blocker infliximab. Moreover, we investigated whether infliximab administration alters circulating leptin and visfatin concentrations in this series of 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 30 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 (26). 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, adipokines and biomarkers of endothelial cell activation in patients with RA (27-29).

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 (30).

A clinical index of disease activity (Bath Ankylosing Spondylitis Disease Activity Index – BASDAI – range of 0 to 10) (31) 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.

The main demographic, clinical and laboratory data of this series of 30 AS patients at the time of the study are shown in Table I. Since at that time all

Table I. Demographic, clinical and laboratory data of 30 patients with ankylosing spondylitis.

Variable	
Mean age (years) ±SD	
At the time of study	50.5 ± 14.8
At the time of onset of symptoms	28.2 ± 10.4
Delay to the diagnosis (years) ±SD	11.5 ± 9.0
Men/women	21/9
Mean disease duration (years) ±SD*	22.0 ± 13.2
History of classic cardiovascular risk factors	
Hypertension	12 (40.0%)
Dyslipidaemia	11 (36.7%)
Obesity (BMI >30 kg/m^2)	3 (10.0%)
Current smokers	13 (43.3%)
Mean blood pressure (mm Hg) ±SD*	
Systolic	123.2 ± 18.2
Diastolic	75.7 ± 12.5
Mean body mass index (kg/m^2) ±SD	26.7 ± 3.3
Mean BASDAI ±SD*	2.94 ± 2.11
Mean VAS ±SD*	31.1 ± 24.2
Hip involvement, n (%)	6 (20.0%)
Synovitis and/or enthesitis in other peripheral joints, n (%)	11 (36.7%)
Anterior uveitis, n (%)	6 (20.0%)
Syndesmophytes, n (%)	10 (33.3%)
Mean CRP (mg/l) ±SD**	
At the time of disease diagnosis	24.0 ± 33.4
At the time of study	6.2 ± 8.7
Mean ESR (mm/1st hour) ±SD***	
At the time of disease diagnosis	30.1 ± 28.2
At the time of study	19.0 ± 15.2
Mean cholesterol or triglycerides*	
Total cholesterol	199.1 ± 30.6
HDL cholesterol	53.2 ± 12.8
LDL cholesterol	126.8 ± 26.5
Triglycerides	94.0 ± 56.7
Mean fasting serum glucose (mg/dl) ±SD*	92.8 ± 8.6
HLA-B27 positive (n=27)	20 (74.1%)

*At the time of the study. **Normal value <5 mg/l. ***Normal value < 20 mm/1st hour.
BASDAI: Bath ankylosing spondylitis disease activity index; BMI: body mass index; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; HLA: human leukocyte antigen; LDL: low-density lipoprotein; SD: standard deviation; VAS: visual analogue scale.

patients were undergoing periodical treatment with the anti-TNF-α monoclonal antibody-infliximab, the mean BASDAI was only 2.94±2.11.

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 reports on the short term effect of infliximab therapy in AS patients (24, 25) were 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 insulin (DPC, Dipesa, Los Angeles, CA, USA), total plasma adiponectin (ELISA, Linco Research, St. Charles, MO, USA; assay sensitivity=0.5 ng/ml; intra-and interassay 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 interassay coefficients of variation were <5% and <7%, respectively) immediately prior to an infliximab infusion (25). Leptin serum levels were determined by a commercially available ELISA (Human Leptin ELISA Kit, EZHL-80SK; assay sensitivity=0.135 ng/ml ±2SD; intra-and interassay coefficients of variation were 3.7% and 4%, respectively) (Linco Research, St. Charles, MO, USA), according to the manufacturer's instructions.

Visfatin serum levels were determined by a commercially available ELISA (Visfatin C-Terminal EIA Kit, EK-003-80; assay sensitivity=2.68n g/ml; intra- and interassay coefficients of variation were <10% and <15%, respectively) (Phoenix Pharmaceuticals, Inc., California, USA), according to the manufacturer's instructions.

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] (24). Subsequently, final blood sampling was performed for determination of leptin and visfatin concentrations immediately after infliximab was administered over 120 minutes.

Statistical analyses

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

The associations between baseline characteristics and serum leptin and visfatin concentrations were assessed by the Student's paired *t*-test for categorical variables. Differences in leptin and visfatin levels between men and women and patients with or without hypertension were assessed by Mann-Whitney U-test.

Leptin and visfatin serum levels before (time 0) and postinfusion (time 120) were compared using the paired Student's *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).

Table II. Partial correlation of serum leptin and visfatin time 0 with selected continuous variables adjusting by age at the time of the study, sex, and classic cardiovascular risk factors in 30 patients with ankylosing spondylitis.

Variable	*r* (with leptin)	*p*-value (with leptin)	*r* (with visfatin)	*p*-value (with visfatin)
Age at the onset of symptoms	-0.195	0.35	0.117	0.56
Disease duration*	0.157	0.45	0.108	0.59
BMI*	-0.233	0.26	0.033	0.87
Systolic blood pressure*	-0.08	0.69	-0.239	0.23
Diastolic blood pressure*	-0.002	0.99	0.002	0.99
BASDAI*	-0.133	0.53	-0.014	0.94
VAS*	-0.199	0.34	-0.051	0.80
ESR* (natural-log-transformed)	0.073	0.73	-0.195	0.33
CRP* (natural-log-transformed)	0.004	0.98	-0.052	0.80
ESR** (natural-log-transformed)	0.117	0.58	-0.067	0.74
CRP** (natural-log-transformed)	0.113	0.59	0.126	0.53
Total cholesterol* (natural-log-transformed)	0.163	0.44	-0.063	0.76
HDL cholesterol* (natural-log-transformed)	0.151	0.47	0.006	0.98
LDL cholesterol* (natural-log-transformed)	0.062	0.77	-0.149	0.46
Triglycerides* (natural-log-transformed)	0.103	0.62	0.067	0.74
Serum glucose* (natural-log-transformed)	0.131	0.53	0.316	0.11
HOMA-IR*	0.258	0.21	0.493	0.009
QUICKI*	-0.249	0.23	-0.294	0.14
Resistin at time 0	0.114	0.62	-0.006	0.98
Adiponectin at time 0	-0.179	0.39	-0.115	0.58
Leptin at time 0	–	–	0.232	0.26
Visfatin at time 0	0.232	0.26	–	–

*At the time of the study. **At the time of disease diagnosis. BASDAI: Bath ankylosing spondylitis disease activity index; BMI: body mass index; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; LDL: low-density lipoprotein; QUICKI: quantitative insulin sensitivity check index; VAS: visual analogue scale.

Results

Relationships of demographic features, inflammation and adiposity with circulating leptin and visfatin concentrations

Leptin and visfatin concentrations did not show significant correlation with age at the onset of symptoms or at the time of the study (Table II). Significant differences in leptin concentrations between men (8.85±5.31 ng/ml) and women (18.96±9.72 ng/ml) were observed (*p*=0.001) (Table III). However, we did not find differences in visfatin levels according to sex. Also, no correlation between CRP and ESR at the time of the study or at the time of disease diagnosis and leptin and visfatin concentrations was seen. Likewise, in this series

Table III. Differences in basal leptin and visfatin (time 0) according to categorical variables.

Variable	Category	Leptin: mean±SD	*p*-value	Visfatin: mean±SD	*p*-value
Sex	Men	8.85 ± 5.31	0.001	2.07 ± 1.41	0.18
	Women	18.96 ± 9.72		1.41 ± 0.52	
Arterial hypertension	Yes	11.07 ± 7.85	0.58	1.71 ± 0.99	0.57
	No	12.87 ± 8.90		1.98 ± 1.40	
Dyslipidaemia	Yes	11.92 ± 8.09	0.93	1.36 ± 0.53	0.09
	No	12.21 ± 8.78		2.17 ± 1.44	
Obesity	Yes	12.24 ± 7.40	0.96	1.22 ± 0.53	0.35
	No	12.08 ± 8.61		1.94 ± 1.28	
Current smoker	Yes	10.07 ± 5.35	0.31	1.90 ± 1.35	0.90
	No	13.41 ± 9.77		1.84 ± 1.19	
Hip involvement	Yes	11.87 ± 8.50	0.95	1.66 ± 0.51	0.65
	No	12.15 ± 8.53		1.92 ± 1.37	
Synovitis and/or enthesitis in other peripheral joints	Yes	11.12 ± 6.99	0.65	1.44 ± 0.48	0.15
	No	12.64 ± 9.18		2.12 ± 1.47	
Anterior uveitis	Yes	14.05 ± 10.08	0.57	1.26 ± 0.16	0.19
	No	11.67 ± 8.14		2.02 ± 1.35	
Syndesmophytes	Yes	14.93 ± 7.98	0.19	1.89 ± 0.79	0.95
	No	10.52 ± 8.37		1.86 ± 1.43	
HLA-B27	Positive	12.62 ± 9.33	0.37	1.70 ± 0.78	0.36
	Negative	9.15 ± 5.45		2.23 ± 2.21	

HLA: human leukocyte antigen; SD: standard deviation.

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

	Basal (time 0)	Postinfusion (time120)	*p*-value
Leptin			
Mean ±SD (ng/ml)	12.10±8.36	11.15±8.22	0.26
(Median; IQ range)	11.61 (5.12–16.18)	8.09 (4.68–15.30)	
Visfatin			
Mean ±SD (ng/ml)	1.87±1.24	2.16±1.75	0.26
(Median; IQ range)	1.33 (1.13–2.03)	1.53 (1.12–2.71)	

SD: standard deviation. IQ: interquartile.

that included 90% of normal-weighted AS patients, no significant correlation between leptin or visfatin serum levels and BMI was observed (Table II).

Relationships of leptin and visfatin concentrations with metabolic syndrome features other than adiposity

No significant correlation between leptin and visfatin concentrations with systolic or diastolic blood pressure, total cholesterol, HDL and LDL-cholesterol, triglycerides and glucose levels was observed (Table II). In keeping with these observations, no significant differences in leptin and visfatin concentrations were seen when patients were stratified according to the presence or absence of hypertension and dyslipidemia (Table III). Nevertheless, a significant correlation between visfatin concentrations and insulin resistance (HOMA at the time of the study) was found (r=0.493; *p*=0.009) (Table II).

Relationships of leptin and visfatin concentrations with other recorded baseline characteristics

Circulating leptin and visfatin concentrations did not correlate with disease duration, BASDAI and VAS spinal pain at the time of the study (Table II). Likewise, no differences in leptin and visfatin 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). Likewise, no significant differences in leptin and visfatin levels were observed when AS patients were stratified according to the presence or absence of hip involvement or synovitis and/or enthesitis in other peripheral joints (Table III).

Changes in leptin and visfatin concentrations upon infliximab therapy

Leptin and visfatin concentrations did not change before and after infliximab infusion (Table IV), and baseline leptin concentrations were not correlated with visfatin levels obtained immediately before infliximab infusion (Table II). Also, no correlations between leptin and visfatin and adiponectin and resistin levels prior to infliximab infusion were observed (Table II). Correlations of post infliximab circulating leptin and visfatin concentrations with the baseline recorded characteristics did not differ from the correlations of baseline circulating leptin and visfatin concentrations (obtained at time 0) with the baseline recorded characteristics (data not shown).

Discussion

Anti-TNF-α therapy has proved to be effective for patients with AS and other spondyloarthropathies (32-34). This fact may explain the low disease activity observed at the time of the study in this series of AS undergoing infliximab treatment.

Adipokines are involved in the regulation of inflammation (11). Elevated serum concentration of leptin has been found in patients with myocardial infarction and stroke independently of traditional CV risk factors and obesity status (35). Moreover, it has been proposed that leptin plays a pathogenic role in atheromatous plaques, due to its positive association with CRP and soluble IL-6 receptor (36). Since AS has been associated with accelerated atherosclerosis and increased incidence of myocardial infarction (2), it may be of interest to study the potential association of leptin with inflammation and other factors associated with CV disease such as metabolic syndrome and classic CV risk factors in patients with AS.

Although IL-6 and BASDAI were found to correlate with leptin levels in Korean AS patients (12), as observed in other reports (13, 22), in our cohort of AS patients undergoing periodical anti-TNF-α therapy, we did not observe correlation between serum leptin levels and clinical and laboratory parameters of disease activity and inflammation. These observations were in keeping with a former study of our group that also reached the same results in patients with severe RA on periodical treatment with the anti-TNF-α-blocker infliximab and ongoing disease activity (37).

Plasma leptin concentration is directly related to the degree of obesity and is higher in women than in men of the same BMI (38). In accordance with these observations, in our series of non-diabetic and in most cases normal-weighted AS patients the only difference was an increase of leptin in women when compared with men. Nevertheless, no correlation between leptin and CV risk factors and variables associated with metabolic syndrome was found.

Kim *et al*. have recently reported an association between the presence of syndesmophytes and leptin levels in Korean men with AS patients (39). It was not the case in our series, as we did not observe an association between leptin levels and specific clinical features of AS patients.

The present study showed that in AS patients on periodical treatment with the anti-TNF-α-blocker infliximab, there was no correlation between serum visfatin levels and clinical and laboratory parameters of disease activity and inflammation. Similarly, in a series of 26 AS patients with mild to moderate disease activity, baseline levels of visfatin did not correlate with markers of disease activity, functional status or acute-phase reactants (22). In the same series (22), baseline levels of visfatin did not predict the change of disease activity or functional ability after 3 months of intensive physiotherapy. As described for leptin (37), no correlation between visfatin levels and disease activity or markers of inflammation was found in patients with severe RA on periodical treatment with the anti-TNF-α-blocker infliximab (40).

Metabolic syndrome features are frequently observed in patients with AS (41, 42). Visfatin promotes adipogenesis (16, 43). However, we do not fully understand what would be its physiological role and clinical relevance in the setting of inflammatory rheumatic diseases. In this regard, in contrast to what was reported in non-rheumatic subjects with a wide range of obesity (21), levels of visfatin did not correlate with BMI in our series of mostly non-obese infliximab treated RA patients (40) and in the present series of AS patients undergoing infliximab therapy. Human obesity-related diabetes and the accompanying metabolic disorders have been specifically linked to increased visceral adipose tissue mass. Visfatin is produced by visceral adipose tissue and also has insulin-mimetic actions (17, 43). However, the relationship between visfatin levels and insulin resistance and other features associated with metabolic syndrome in patients with chronic inflammatory rheumatic diseases requires further elucidation. In this regard, although most AS patients from our series were not obese and the stratification of patients according to BMI did not disclose significant differences, in the present the study we observed a significant correlation between circulating visfatin and insulin resistance determined by HOMA. Similar results were found in a series of 21 obese women, which showed a significant correlation between serum concentrations of visfatin and insulin (44). Also, visfatin was found to be associated with insulin resistance in lean women with polycystic ovary syndrome (45). Although visfatin levels were found to be increased in individuals with hyperglycaemia (46), we could not explore this situation in our study as patients with diabetes were excluded during the period of recruitment.

AS belongs to a group of disorders called seronegative spondyloarthropathies, which includes also psoriatic arthritis and inflammatory bowel disease (IBD). Common pathogenic mechanisms are likely to be shared by these diseases. With respect to this, subclinical atherosclerosis and increased incidence of CV mortality has also been observed in patients with psoriatic arthritis (47-49). In line with this, high serum leptin levels were observed in obese patients with psoriatic arthritis (50). On the other hand, visfatin levels were elevated in patients with active IBD but not in those in remission (51). With respect to leptin in IBD, a significant increase in serum leptin levels was found in patients with acute ulcerative colitis when compared with controls (52). However, as observed in our series of AS patients, no correlation between leptin levels and BMI was found (52).

Regarding the potential effect that anti-TNF-α therapy could make on leptin and visfatin concentrations, we found that infliximab infusion did not alter circulating levels of these adipokines in AS patients. Likewise, in a series of 30 AS patients, serum levels of leptin did not change significantly after a 6-month infliximab treatment (15). These results are in agreement with Popa *et al*. that reported no short- (at 2 weeks) or long-term effect (at 6 months) of TNF-α blockade on circulating leptin concentrations in RA (53).

A potential limitation of our study was that our research was cross-sectionally designed and, therefore, the findings should be interpreted as hypothesis generating rather than definitive. Because of that, 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 leptin and visfatin serum levels do not correlate with disease activity or systemic inflammation. Nevertheless, visfatin concentration correlates with insulin resistance. This finding may indicate a potential role for visfatin in the pathogenesis of the CV disease in AS. However, further studies are needed to elucidate the implication of adipokines in the CV disease of patients with AS.

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