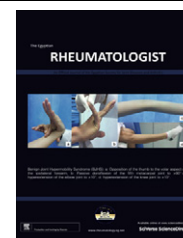




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ORIGINAL ARTICLE

Influence of adipocytokines and IL-6 on ankylosing spondylitis disease activity and functional status

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KEYWORDS

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Abstract *Aim of the work:* This study aimed to assess serum levels of some adipocytokines (leptin, adiponectin and resistin) and IL-6 in patients with ankylosing spondylitis (AS) to evaluate their relationship to disease activity and functional capacity.

Patient and method: Twenty-five AS patients were enrolled. Body mass index (BMI), Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI) and acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, were assessed. Serum leptin, adiponectin, resistin and interleukin (IL)-6 levels were determined using enzyme-linked immunosorbent assay (ELISA).

Results: The mean levels of leptin (9.1 ± 3.9 ng/ml), resistin (2.27 ± 1.15 ng/ml) and IL-6 (9.2 ± 5.8 pg/ml); were significantly elevated in patients with AS compared to the controls ($p = 0.000$, $p = 0.0028$ and $p = 0.000$, respectively). Only serum leptin levels correlated significantly with IL-6 ($p = 0.004$), and both serum leptin and IL-6 levels correlated significantly with BASDAI ($p = 0.02$ and $p = 0.005$, respectively), ESR ($p = 0.04$) and CRP ($p = 0.01$ and $p = 0.006$, respectively) in AS patients. Serum resistin did not correlate with any of the AS disease parameters, whereas, serum adiponectin neither significantly elevated nor correlated with any of these parameters.

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Conclusion: The associations of significantly increased levels of serum leptin and IL-6 with AS disease activity parameters give clues to their role in the inflammatory process of the disease. Failure to find any correlation between high serum resistin levels and AS disease activity parameters is suggestive of its role in the pathogenesis rather than disease activity.

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1. Introduction

White adipose tissue is an emerging active participant in regulating physiologic and pathologic processes, including immunity and inflammation [1,2].

Adipose tissue produces a variety of pro-inflammatory and anti-inflammatory factors, including the adipocytokines leptin, adiponectin, resistin, and visfatin, as well as cytokines and chemokines, such as tumor necrosis factor- α (TNF- α), interleukin (IL)-6, and others [3].

The influence of these adipocytokines on immunity and inflammation has been well documented [4]. Leptin has systemic effects apart from those related to energy homeostasis, including regulation of neuroendocrine, reproductive, hematopoietic and immune function [5].

It is generally accepted that leptin displays pro-inflammatory effects, while adiponectin is considered to primarily act as an anti-inflammatory molecule [6]. It has been reported that leptin receptors are expressed on B and T-cells. Leptin may stimulate T cell proliferation, promote a Th1 response, influence T-cell activation, and activate macrophages and monocytes, thereby enhancing their phagocytic activities [7]. Adiponectin exerts a variety of anti-inflammatory activities, interfering with the macrophage function by inhibiting phagocytosis, IL-6 or TNF- α production, reducing T-cell function, and promoting the release of IL-10 and IL-1 receptor antagonist [8].

Resistin is an adipocytokine initially described as a polypeptide produced by adipose tissue. It is regulated by peroxisome proliferator-activated receptor gamma providing a link between obesity and insulin resistance [9]. Later, it has been identified that while resistin levels were very low in human adipocytes, its level was higher in mononuclear leukocytes, macrophages, spleen, and bone marrow cells [10]. Thus, it was suggested that resistin levels had a better relationship with subclinical inflammation than with insulin resistance [11].

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the sacroiliac joints and spine; some patients may also have extra-articular manifestations [12,13].

It is suspected that upregulation of pro-inflammatory cytokines is effective in the immunopathogenesis of AS. It is found that TNF- α and IL-6 levels are higher in AS patients than in healthy people [14] with some of them showing good correlation with the parameters reflecting disease activity [15].

Leptin increases the production of TNF- α , which suppresses the transcription of adiponectin in adipocytes, and treatment of cultured macrophages with adiponectin markedly inhibits their phagocytic activity and production of TNF- α in response to stimulation with lipopolysaccharide [6,16]. Few studies have evaluated serum levels of leptin and adiponectin in AS. The aim of this study was to assess serum levels of

leptin, adiponectin, resistin, and IL-6 in patients with AS to evaluate their relationship to disease activity and functional capacity.

2. Patients and methods

2.1. Patients

Twenty-five patients with definite AS (23 males and 2 females), diagnosed according to the modified New York criteria of AS [17] were selected from the attendants of the rheumatology and rehabilitation clinic at Benha University Hospitals. Six patients (24%) were on methotrexate and NSAIDs therapy and 15 (60%) were receiving NSAID and sulfasalazine. Three patients (12%) were receiving only NSAIDs. Two patients were on no medication. Twenty (18 males and 2 females) sex, age and body mass index- matched healthy subjects were recruited as controls.

The research protocol was approved by the Ethics Committee of our institution and informed written consents were obtained from all participants. We excluded patients with diabetes mellitus, other endocrine disorders, chronic liver disease, chronic renal disease, recent history of glucocorticoids intake and postmenopausal status.

2.2. Clinical and physical measurement

Patients were clinically evaluated, the axial as well as the peripheral joints were assessed. Lumbar schober, occiput-wall distance and chest expansion were measured as part of the clinical assessment. Patients were evaluated using the Bath AS disease activity index (BASDAI) [18] and Bath AS Functional Index (BASFI) [19]. Waist circumference (cm) and BMI calculated as weight/height² (kg/m²) were obtained.

2.3. Biochemical assessments

Venous blood samples were obtained after overnight fasting at the same time of physical assessment from all patients and controls.

The following assessments were done:

- A citrated blood sample was used for the assay of erythrocyte sedimentation rates (ESR) by the modified Westergren method.
- Serum was separated from another plain (no additive) tube for measurement of C-reactive protein (CRP) levels by immunonephelometry using Turbox plus instrument.
- Serum concentrations of fasting glucose, total cholesterol and triglycerides were determined by Cobas Integra A 400 clinical chemistry analyzer (Roche).
- High-density lipoprotein cholesterol (HDL-C) was determined by kits supplied from Sigma diagnostics.

- Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula [20].
- An aliquot of serum was stored at -20°C until other investigations are assayed.
- Serum leptin and adiponectin were measured by specific ELISA assay using material and protocols supplied by the provider Biovendor (Heidelberg, Germany).
- Serum resistin and IL-6 were determined by ELISA assay by kit supplied from Abcam (Cambridge, UK).

2.4. Radiological examination

Plain radiographic examination was performed for the pelvis and entire spine for all patients as a part of assessment of AS, in addition to plain X-ray for any affected joints.

Statistical analysis was performed using Statistical Package for Social Sciences software (SPSS), version 13.0. Quantitative variables (demographic, clinical and laboratory) were presented as the mean \pm SD. Student's (*t*) test was used to compare means. Relationships between parameters were analyzed using Pearson correlation coefficients (*r*). *P* value less than 0.05 was considered significant.

3. Results

- Patient characteristics are represented in (Table 1): The mean disease duration was 45.2 ± 11.2 months, all patients (100%) had axial articular involvement, 6 patients (24%)

had peripheral articular manifestations, 8 patients (32%) had uveitis while, only one patient (4%) had cardiac involvement in the form of aortic regurgitation. The mean value of lumbar flexion was 3.08 ± 2.19 and the mean value of occiput-wall distance (cm) was 4.6 ± 3.5 . Chest expansion (cm) value was determined as 3.5 ± 1.5 .

- The mean BASDAI was 5.1 ± 1.7 and the mean BASFI was 5.6 ± 1.9 . As regards inflammatory markers, both ESR and CRP were significantly higher in patients (29.2 ± 9.1 mm/h) and (15.4 ± 4.8 mg/l) than controls (13.4 ± 2.1 mm/h) and (5.9 ± 2.2 mg/l), respectively.
- There was a statistical significant increase in serum leptin ($p = 0.000$), resistin ($p = 0.0028$) and IL-6 ($p = 0.000$) levels in patients than in controls, while, there was an insignificant difference in adiponectin serum levels between patients and controls ($p = 0.19$) (Table 2). AS patients with peripheral articular manifestations had significantly higher serum leptin (10.9 ± 1.9 ng/ml) and IL-6 (11.8 ± 1.01 pg/ml) levels compared to those without peripheral involvement (7.6 ± 3.3 ng/ml and 8.1 ± 4.2 pg/ml respectively), where $p = 0.03$ and $p = 0.046$, respectively (Fig. 1).
- Significant correlations of serum leptin levels with anthropometric measurements ($p = 0.007$ and $p = 0.01$ for BMI and waist, respectively), BASDAI ($p = 0.02$), ESR ($p = 0.04$), CRP ($p = 0.01$) and IL-6 ($p = 0.004$) but not with BASFI ($p = 0.19$) were found. Whereas, there were significant correlations of serum IL-6 levels with BASDAI ($p = 0.005$), BASFI ($p = 0.01$), ESR ($p = 0.04$) and CRP ($p = 0.006$) but not with anthropometric measurements

Table 1 Demographic, clinical and laboratory characteristics of studied groups.

Parameters	Groups		<i>t</i>	<i>p</i>
	AS patients (no = 25)	Control group (no = 20)		
Age (years)	29.11 ± 7.86	32.12 ± 6.41	1.42	0.17
Disease duration (months)	45.2 ± 11.2	–	–	–
<i>Anthropometric measurements</i>				
BMI (kg/m ²)	25.07 ± 3.04	26.22 ± 2.66	1.35	0.19
Waist (cm)	78.29 ± 8.2	79.3 ± 7.1	1.06	0.29
<i>Articular manifestations</i>				
Axial	25 (100%)	–	–	–
Peripheral	6 (24%)	–	–	–
<i>Extraarticular manifestations</i>				
Uveitis	8 (32%)	–	–	–
Cardiac	1 (4%)	–	–	–
BASDAI	5.1 ± 1.7	–	–	–
BASFI	5.6 ± 1.9	–	–	–
<i>Lipid profile</i>				
Total cholesterol (mg/dl)	151.22 ± 7.7	154.41 ± 8.9	1.32	0.2
HDL cholesterol (mg/dl)	54.23 ± 3.7	51.5 ± 9.2	1.25	0.18
LDL cholesterol (mg/dl)	77.34 ± 5.12	79.4 ± 7.4	1.07	0.28
TG (mg/dl)	82.14 ± 7.2	84.33 ± 9.7	0.84	0.39
ESR (mm/1st h)	$29.2 \pm 9.1^*$	13.4 ± 2.1	8.4	0.000
CRP (mg/l)	$15.4 \pm 4.8^*$	5.9 ± 2.2	8.1	0.000

AS, ankylosing spondylitis; BMI, body mass index; BASDAI, bath ankylosing spondylitis disease activity index; BASFI, bath ankylosing spondylitis functional index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

* Significantly different.

Table 2 Adipocytokines and IL-6 serum levels in AS patients and control.

Parameters	Groups		<i>t</i>	<i>p</i>
	AS patients (no = 25)	Control group (no = 20)		
Leptin (ng/ml)	9.1 ± 3.9*	4.3 ± 3.5	4.36	0.000
Adiponectin (ug/ml)	10.44 ± 0.63	10.21 ± 0.52	1.35	0.19
Resistin (ng/ml)	2.27 ± 1.15*	1.42 ± 0.36	4.11	0.0028
IL-6 (pg/ml)	9.2 ± 5.8*	2.3 ± 1.9	5.57	0.000

IL-6, interleukin-6.

* Significantly different.

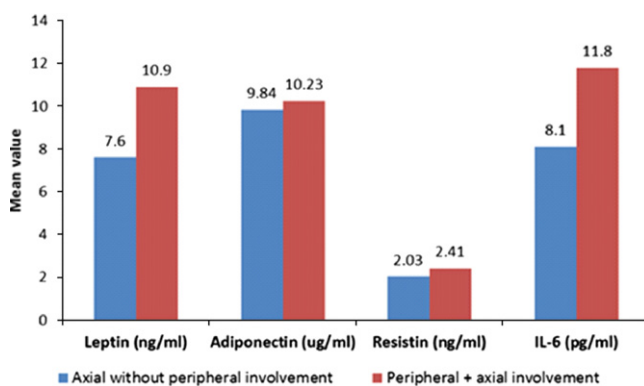


Figure 1 Serum adipocytokines and IL-6 levels in AS patients with and without peripheral articular involvement.

($p = 0.31$ and $p = 0.33$ for BMI and waist, respectively). Consistently, we did not find any correlations of either adiponectin or resistin serum levels with any of the disease related variables ($p > 0.05$) (Table 3).

4. Discussion

This study aimed to assess levels of leptin, adiponectin, resistin and IL-6 in patients with AS to evaluate their relationship to disease activity and functional capacity.

The results of our study demonstrated that serum levels of leptin, resistin and IL-6 were significantly increased in AS patients compared to healthy controls. Serum leptin levels also significantly correlated with anthropometric measurements, BASDAI, BASFI, ESR, CRP and IL-6.

Increased serum levels of different pro-inflammatory cytokines in AS patients have been reported with good correlation with the disease activity parameters [15,21].

Many different tissues secrete IL-6 [22], including adipose tissue [23] and its pivotal role in the pathogenesis of AS has been suggested. Elevated levels of IL-6 and TNF- α have been found in the sera of AS patients in a study done by Gratacos et al. [21], verifying good correlation between IL-6 and disease activity.

Our results were in agreement with those of Park et al. [24], who found that patients with AS had significantly elevated serum levels of IL-6 correlating significantly with disease activity (BASDAI) and CRP while non significantly correlated with ESR.

The significantly higher leptin levels in our study could be explained by the results obtained by Park et al. [25], who

demonstrated increased expression of leptin, IL-6 and TNF- α mRNA in peripheral blood mononuclear cells (PBMCs) from patients with AS and reported that stimulation of PBMCs with leptin significantly induced dose-dependent increases of IL-6 and TNF- α production in PBMCs suggesting a role of leptin in the pathogenesis of the disease.

Contrarily, Derdemezis et al. [26], observed no difference in leptin levels between controls and AS patients and found no correlation with any disease parameters. In addition, Sari et al. [27], observed that leptin levels were significantly lower in AS patients than in controls and reported a significant correlation with CRP supporting the theory that chronic inflammation reduces the body fat content and lower leptin production by adipocytes, as adipose tissue is the main source of serum leptin.

This incongruity could be explained by differences in some related factors, such as gender, menopausal status, BMI and medications which can potentially alter leptin levels and disease activity of AS.

Trujillo and his colleagues [28], demonstrated that increased local IL-6 concentration can increase leptin production in human adipose tissue. Baumann et al. [29], supported the role of leptin in inflammatory responses by signaling capabilities of leptin receptor on IL-6-type cytokine receptors.

Moreover, Tartaglia et al. [30], reported sequence homology between leptin receptor and members of the class I cytokine receptor superfamily, including the receptor for IL-6.

Furthermore, for AS patients with peripheral articular manifestations, Leptin and IL-6 serum levels were significantly higher than those of patients with only axial involvement.

Concordant to our results, Huang et al. [31], observed a significant increase of IL-6 serum levels in AS female patients with syndesmophytes.

In this study, we found insignificant differences ($p = 0.19$) between patients and controls as regards adiponectin serum levels as well as no correlations with any of the disease related parameters.

Our results are in accordance with those of Toussiro et al. [32], who found normal adiponectin serum levels in their AS patients but failed to find any correlation between circulating adiponectin and BMI, ESR, CRP or BASDAI in those patients.

In the same context, Fantuzzi [8], reported that pro-inflammatory cytokines including (TNF- α , IL-6) inhibit the production of adiponectin that explains the inverse correlation between adiponectin levels and inflammatory markers found in his study. Also, Fernandez-Real and his associates [33] suggested that adiponectin is related to the inflammatory process by inducing the release of IL-10 and IL-1 receptor antagonist.

Derdemezis et al. [34], found elevated adiponectin levels, not correlated with any disease parameter in AS patients.

Table 3 Correlations of adipocytokines and IL-6 serum levels with clinical and laboratory parameters in AS patients.

Parameter	Protein							
	Leptin (ng/ml)		Adiponectin (ug/ml)		Resistin (ng/ml)		IL-6 (pg/ml)	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
<i>Anthropometric measurements</i>								
BMI (kg/m ²)	0.52	0.007*	0.28	0.16	0.25	0.17	0.15	0.31
Waist (cm)	0.48	0.01*	0.21	0.19	0.26	0.17	0.12	0.33
BASDAI	0.45	0.02*	0.17	0.29	0.27	0.16	0.58	0.005*
BASFI	0.21	0.19	0.09	0.8	0.24	0.16	0.49	0.01*
ESR (mm/1st h)	0.4	0.04*	0.42	0.16	0.24	0.16	0.4	0.04*
CRP (mg/l)	0.48	0.01*	0.26	0.17	0.15	0.31	0.55	0.006*
IL-6 (pg/ml)	0.61	0.004*	0.29	0.26	0.28	0.26		

BMI, body mass index; BASDAI, bath ankylosing spondylitis disease activity index; BASFI, bath ankylosing spondylitis functional index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6.

* Significantly different.

These results are in line with those reported in previous studies done on RA patients [34–36] and SLE patients [37–39]. These paradoxical results were based on the fact that under certain circumstances adiponectin seems to induce the expression of TNF- α [40], contradicting its anti-inflammatory role and rendering a question regarding its exact action.

Our AS patients exhibited a significant elevation in serum resistin levels, however we failed to find any correlation between its levels and disease related parameters.

Patel et al. [10], reported that resistin mRNA is detectable in circulating mononuclear cells suggesting the role of human resistin in the inflammatory process.

Our results are consistent with those of Kocabas et al. [41], who found that the serum resistin levels were significantly increased in patients with AS compared to healthy people, but did not correlate with activity markers including ESR, CRP and BASDAI.

In conclusion, adipocytokines have different roles in inflammatory sequences occurring in AS. Leptin, together with IL-6, correlated well with disease activity parameters giving clues to their pro-inflammatory role in the disease.

Failure to find any correlation between high serum resistin levels and AS disease activity parameters is suggestive of its role in the pathogenesis rather than disease activity. Adiponectin is only a bystander in AS and its role in this disease process is yet to be clarified.

Conflict of interest

All the authors responsible for this work declare no conflict of interest.

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