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Visceral Fat Reflects Disease Activity in Patients with Ankylosing Spondylitis

Abstract

Purpose: Response to infliximab treatment diminishes as body mass index (BMI) increases in patients with ankylosing spondylitis (AS). The purpose of the study was to determine if diminished response to infliximab treatment in patients with AS could be associated with increased visceral adipose tissue rather than increased BMI.

Methods: Twenty six AS patients (21 males and five females) who fulfilled the modified New York criteria and who were currently receiving infliximab treatment were enrolled in the study. Pain was measured by the visual analogue scale (VAS). The disease activity and functional status were assessed by the Bath AS Disease Activity Index (BASDAI) and the Bath AS Functional Index (BASFI). The Bath AS Metrology Index (BASMI) was used to evaluate mobility restrictions. Weight and visceral body composition were measured without shoes in light indoor clothes using a bio-impedance meter.

Results: There was a significant correlation between visceral adipose tissue amount and disease activity under infliximab treatment. In correlation analysis, visceral fat showed significant correlations between BASDAI ($r=0.545$, $p=0.004$) and VAS ($r=0.458$, $p=0.019$). Total body fat also showed a significant correlation with BASDAI ($r=0.463$, $p=0.017$).

Conclusion: A significant correlation was found between visceral adipose tissue amount and disease activity in patients with AS.

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Excessive fat is associated with overweight and obesity [1]. One of the most widely used population measure of obesity is the body mass index (BMI). Adipose tissue can exert endocrine and immune effects on multiple organs via the release of adipocytokines [2] that are suspected to contribute to the pathogenesis of several inflammatory conditions [3]. Furthermore, visceral fat has been shown to secrete far greater amounts of adipocytokines and inflammatory biomarkers compared with subcutaneous adipose tissue [4-6]. The association between chronic inflammatory rheumatic diseases, such as ankylosing spondylitis (AS), and visceral adiposity is a relevant issue. A recent report has suggested that an increase in BMI negatively influences the response to infliximab treatment in patients with AS [7].

We aimed to investigate whether there is a correlation between visceral adipose tissue amount and disease activity in patients with AS.

Materials and Methods

Study population

Twenty six patients between the ages of 18 and 68 years, who presented to the Dicle University School of Medicine, Department of Physical Medicine and Rehabilitation outpatient clinic and were diagnosed with definite AS according to the 1984 Modified New York Criteria, were enrolled in our study [8]. The study protocol was approved by the Ethics Committee of Dicle University and every test subject signed a consent form. The data were obtained by a combination of questionnaire, physical examination of musculoskeletal system, sampling of blood and total body fat measurement. The procedures were in accordance with the ethical standards of the Helsinki Declaration of 1983. Patients with any kind of collagen tissue disorders or any other inflammatory articular diseases, malignancies, diseases of the central nervous system, chronic kidney/liver and thyroid diseases other than AS, and those who were pregnant were excluded from the study. The demographic and clinical characteristics of the patients, the disease duration (disease duration is defined as the duration since the onset of the first symptoms of AS) and medications (non-steroidal anti-inflammatory drugs (NSAIDs) and anti-tumour necrosis factor (TNF) therapy) were recorded. Pain levels (100 mm visual analogue scale (VAS)) were also noted. Serum C-reactive protein (CRP) levels were measured by nephelometry (mg/dl). The disease activity was evaluated using the Bath AS disease activity index (BASDAI) [10]. The functional statement was evaluated with the Bath AS functional index (BASFI) [11]. The scores of the spinal and hip measurements were deter-

mined through the Bath AS metrology index (BASMI) [12]. BMI was calculated by weight in kilograms divided by height in square meters. According to the WHO criteria, normal BMI was defined as a BMI < 25 kg/m²; overweight, as a BMI of 25 to 30 kg/m²; and obesity, as a BMI > 30 kg/m² [1].

Bioimpedance meter analysis

Weight and visceral body composition were measured without shoes in light indoor clothes using a bio-impedance meter (Omron BF 500; Omron Corp. Kyoto, Japan). Waist circumference was measured with a tape, the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Body mass index was calculated as weight divided by height squared (kg/m²).

Statistical evaluation

Statistical Package for Social Sciences Software (SPSS 12, Chicago, IL, USA) was used for analysis. Descriptive parameters were shown as mean $\pm$ standard deviation or as percentages. Spearman's correlation analysis was applied to examine the relationship between the body fat composition and AS activity. The covariates included in the analysis were BASDAI, VAS, BASFI, BASMI age, gender, BMI, waist circumference, visceral fat level, total body fat, total body mass, glucose and C reactive protein (CRP). The data were considered as significant when $p < 0.05$.

Results

The final cohort consisted of 26 participants (21 males, five females) with a mean age of 36 ± 12 years. The median disease duration was 5.53 years and median level of CRP was 1.97 mg/dl. The baseline demographic and clinical features of the AS patients are summarized in Table 1. The age and sex adjusted partial correlation analysis revealed that BMI, waist circumference and visceral fat level were correlated with the BASDAI, VAS, BASFI, BASMI scores (Table 2). In the correlation analysis, visceral fat showed significant correlations between BASDAI ($r=0.545$, $p=0.004$) and VAS ($r=0.458$, $p=0.019$). Total body fat also showed a significant correlation with BASDAI ($r=0.463$, $p=0.017$).

Discussion

In the present study, increased BMI, waist circumference and visceral fat level were correlated with the BASDAI, VAS, BASFI, BASMI scores in patients with AS.

TABLE 1. Characteristics of 26 ankylosing spondylitis patients on infliximab

Age (years) [IQR]	36 (18-68)
Male gender, n(%)	21(80.8)
Disease duration (years), median [IQR]	5.53(1-18)
BASDAI (0 to -100 mm), median [IQR]	2.46(0-6)
VAS pain (0 to 100 mm), median [IQR]	33.07(0-75)
Use of NSAIDs (% of maximal dose), mean (SD)	3.8
CRP (mg/dl), median [IQR]	1.97(0.11-11.6)

AS, ankylosing spondylitis; BASDAI; Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range, NSAID, nonsteroidal anti-inflammatory drug; VAS, visual analogue scale.

Ankylosing spondylitis is an inflammatory rheumatic disease that is associated with a predominant loss of appendicular lean mass, while body fat usually remains unaltered [13, 14]. In addition to disease activity, proinflammatory cytokines, especially TNF- α , are linked to alterations in body composition in patients with AS [13]. Some studies have shown significant increases in body weight and fat mass in AS patients receiving anti-TNF- α treatment [15, 16]. Long-term TNF- α inhibition in AS is associated with a significant gain in fat mass, with a shift to the visceral region [16]. The excess adipose tissue in these individuals may have immunomodulating properties and pharmacokinetics consequences [17].

Many studies have previously reported that visceral adipose tissue has a stronger association with metabolic risk factors than does subcutaneous adipose tissue [18-20]. Visceral fat explants have been shown to secrete far greater amounts of CRP, IL-6, TNF- α , VEGF, angiotensinogen and PAI-1, compared with dissected subcutaneous adipose tissue [4-6]. When compared with BMI-matched controls with increased subcutaneous fat deposition, patients with increased amounts of abdominal fat have increased circulating levels of CRP, TNF- α , IL-6, PAI-1, angiotensinogen, increased platelet-activating eicosanoids and increased numbers of activated platelets [5,6,21-23].

The link between metabolic syndrome and rheumatic diseases is also at play in AS. It has been reported that metabolic syndrome and CVDs are more frequent in AS patients compared with healthy controls (46% versus 11%, respectively), even after receiving anti-tumor necrosis factor (anti-TNF) therapy [24-26].

TABLE 2. Age- and sex-adjusted partial correlation analysis of adiposity parameters with disease activity scores

	BASDAI	VAS	BASFI	BASMI
VF	0.545**	0.458*	0.315	0.359
TBF	0.463*	0.323	0.1	0.167
CRP	0.120	0.33	0.279	0.192
BMI	0.655***	0.552**	0.331	0.316
WC	0.613**	0.515**	0.22	0.306

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Pain Visual Analogue Scale (VAS), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), VF: visceral fat, TBF: total body fat, CRP: C reactive protein, BMI: body mass index, WC: waist circumference, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

A decrease in TNF- α in obese patients, after weight loss with dietary treatment and exercise, has been shown to be related to an improvement in insulin sensitivity [27]. Interestingly, in the same study, basal TNF- α levels correlated with the visceral fat area and not with the subcutaneous fat area (both measured by computed tomography) or BMI [27]. In another study, serum TNF- α bioactivity was increased in obese and type 2 diabetic patients and correlated positively with basal serum C-peptide levels [28]. Also, Dandona et al. showed that serum TNF- α decreased with weight loss in obese patients [29].

Deiuliis et al. [30] reported that obesity in mice and humans actually results in adipose T regulatory cell depletion. T regulatory lymphocytes are responsible for peripheral immune tolerance and are diminished in autoimmune diseases. Lack of T lymphocyte regulation on β -lymphocytes may result in increased autoantibody levels. A recent report suggested that a high the BMI negatively influences the response to infliximab in AS [7]. In another study, many of the inflammatory cytokines (i.e., TNF- α , IL-6) have been shown to promote migration of mesenchymal precursors to adipose tissue depots stimulate adipocyte differentiation in RA [31]. The potential end-result of these processes is an increase in visceral fat. Adipocytes and resident adipose tissue macrophages are an additional source of inflammatory cytokines. Antagonism of TNF- α was successful in reversing these processes in several studies [32-37]. It has also been suggested that fat mass may affect the response to therapy by showing a negative correlation between BMI and response to infliximab in rheumatoid arthritis (RA) [38]. Thus, in our study, we speculated that increased visceral fat is responsible for the blunted effect of biological treatment in AS

patients. Our study further showed that disease activity scores of these patients were correlated with visceral fat tissue.

Limitations of the study

The study consisted of only a small group and did not have a control group. As this was a cross-sectional study, the effect of therapy on visceral fat or effect of visceral fat on response status was not evaluated.

Conclusion

This study provides the first evidence of a significant correlation between the amount of visceral adipose tissue and AS disease activity. Future studies with larger samples with prospective follow-up cohort are needed to determine how this observation should be taken into account for the treatment of AS patients. In addition, more data, including more precise assessment of the fat mass, adipocytokines release and pharmacokinetic study of the drug, are needed to elucidate the mechanism by which fat mass affects response to infliximab in inflammatory rheumatic conditions.

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