Early Increase of Abdominal Adiposity in Patients with Spondyloarthritis Receiving Anti-tumor Necrosis Factor-α Treatment

Ihsane Hmamouchi, Christian Roux, Simon Paternotte, Sami Kolta, Maxime Dougados, and Karine Briot

ABSTRACT. ***Objective.*** Patients with spondyloarthritis (SpA) receiving anti-TNF-α treatment have an increase in fat mass. This may be relevant to cardiovascular risk. The aim of this study was to estimate visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) changes by dual-energy x-ray absorptiometry (DEXA) in patients with SpA under anti-TNF-α therapy.

Methods. We used an ancillary protocol to an open, prospective 2-year followup study of patients with SpA. Waist circumference (WC), body weight, body mass index, VAT, and SAT were measured at baseline, 6 months, and 1 and 2 years. Univariate and multivariate analyses were performed to assess variables associated with VAT and SAT changes.

Results. A total of 85 patients were analyzed. Patients were 39.3 ± 11.4 years old and mean baseline Bath Ankylosing Spondylitis Disease Activity Index was 55.0 ± 20.2. Treatment was effective according to clinical and biological variables, and body weight increased by 0.9 ± 1.7 kg over 2 years. There was a significant gain in VAT after 6 months (13.7 ± 20.6 cm^2, $p < 0.0001$), 1 year (21.0 ± 26.6 cm^2, $p < 0.0001$), and after 2 years (29.1 ± 33.4 cm^2, $p < 0.0001$); and in SAT after 6 months (12.5 ± 27.4 cm^2, $p < 0.0001$), 1 year (27.1 ± 38.2 cm^2, $p < 0.0001$), and after 2 years (31.9 ± 53.2 cm^2, $p < 0.0001$). We could not find any determinant of these changes by multivariate analysis.

Conclusion. In patients with SpA receiving anti-TNF-α therapy, there is an early significant increase in abdominal obesity with significant increase in both VAT and SAT after 1 and 2 years of treatment. Prospective studies are required to investigate the relationship between these changes and cardiovascular risk. (J Rheumatol First Release April 15 2014; doi:10.3899/jrheum.131150)

Key Indexing Terms:
ABDOMINAL ADIPOSITY SUBCUTANEOUS ADIPOSE TISSUE SPONDYLOARTHRITIS
VISCERAL ADIPOSE TISSUE ANTI-TUMOR NECROSIS FACTOR-α

Spondyloarthritis (SpA) is a heterogeneous group of inflammatory rheumatic disorders with mainly axial and sacroiliac but also enthesitic and peripheral involvement[1]. Anti-tumor necrosis factor (TNF)-α therapy induces a significant and sustained reduction in clinical disease activity and systemic inflammation in SpA[2]. We previously showed a significant increase in body weight and total body fat at 1 year and 2 years in patients with SpA receiving anti-TNF-α treatment[3,4]. Whether this increase in body fat reflects increased visceral adiposity or subcutaneous adiposity is currently unknown. The distribution of body fat is more important than the amount of fat for cardiovascular risk. Body fat tissue is distributed into 2 main compartments with different metabolic characteristics: subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). Studies indicate that VAT is highly associated with insulin resistance and cardiovascular diseases (CVD)[5,6]. VAT is a hormonally active tissue, releasing different bioactive molecules and hormones such as adiponectin, leptin, resistin, TNF, and interleukin 6.

Body mass index (BMI) is the most commonly used diagnostic tool for characterizing obesity[7]. Waist-to-hip ratio or waist circumferences (WC) are additional measures used in clinical practice to derive estimates of fat distribution[8]. However, these measures cannot distinguish between lean and fat body mass and they are not accurate enough to reveal differences between subcutaneous and visceral fat compartments[9].

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Dual-energy x-ray absorptiometry (DEXA) is a widespread and validated method for assessment of body composition including body fat. It is less expensive and more accessible than the gold standard imaging methods — computed tomography (CT) and magnetic resonance imaging (MRI)[10,11]. Recently, a new software was developed on DEXA devices allowing the separation, inside a region of interest, of abdominal fat into VAT and SAT[10]. This method was validated through comparison with CT technology[12].

The aim of our present study was to estimate VAT and SAT changes measured by DEXA in patients with SpA receiving anti-TNF-α therapy.

MATERIALS AND METHODS

Study design. This study is an ancillary protocol to an open, prospective, 2-year followup study of patients with SpA in a single tertiary care center, previously published[4]. SpA was defined according to the European Spondyloarthropathy Study Group criteria[13]. Seventy-nine patients (92.9%) had ankylosing spondylitis according to the New York criteria[14] and 6 (7.1)% had peripheral SpA. Also, 79 patients responded to the ASsessments in Ankylosing Spondylitis Working Group (ASAS) axial SpA criteria[15].

Patients. A total of 106 patients were considered, because they required anti-TNF therapy owing to persistent active disease despite an optimal dose of nonsteroidal antiinflammatory drugs and/or treatment with methotrexate or sulfasalazine according to either ASAS criteria or the investigator's opinion, based on the severity of the disease. For our study, we included only 85 patients, because they had baseline and followup measurements on 1 single fan-beam DEXA device equipped with the new software of visceral fat assessment. These 85 patients were the basis of our study.

Measurements. Clinical assessment included demographic data: age, disease duration, and current corticosteroids. The clinical activity and severity of the disease were evaluated every 6 months for 2 years by visual analog scale for global pain (0–100 mm), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Bath Ankylosing Spondylitis Functional Index and by biological markers of inflammation: erythrocyte sedimentation rate (mm/h) and C-reactive protein (mg/l). A BMI > 25 kg/m^2 indicates overweight while a BMI over 30 kg/m^2 indicates obesity[16].

Abdominal adiposity. Body composition (fat and lean masses) was calculated by DEXA (QDR 2000, Hologic). Adipose tissue was calculated in a region of interest (ROI) of 5 cm height at the level of the L4 vertebra. This ROI is placed automatically by the software at a fixed distance from the iliac crests as defined by the operator. The global ROI (rectangular in shape) is divided into 3 rectangles. Manual delineation, using tools provided by the software, was used to position the right and left heights limiting the skin as well as the outer and the inner muscle edges. This leads to separation of SAT, intramuscular adipose tissue, and VAT (Figure 1). The ratio of VAT area/SAT area was also calculated. Greyscale adjustment of the images allowed recognition of air, skin, muscle, and fat. The images were analyzed by 2 readers, following a standardized protocol. WC was also automatically measured by the same software.

Whole-body scans were done at baseline, 6, 12, and 24 months. For 18 patients, body composition measurements were available before the baseline measurements with mean interval duration between both examinations of 8.1 (± 3.55) months. Quality control of the device was done using the manufacturer's spine phantom for quality assurance, and stability monitoring of bone mineral density measurements was performed daily throughout the study according to the manufacturer's recommendations. The phantoms used were those of the manufacturers.

Anti-TNF treatment. All patients were treated as decided by their physician, with etanercept (25 mg twice a week) or infliximab (IFX; 3 or 5 mg/kg/infusion at weeks 0, 2, 6, and thereafter infusions at 6-week or 8-week intervals) continuously over 2 years.

Statistical analysis. Intraclass correlation coefficient (ICC) was used to evaluate the interobserver reproducibility of the analysis of VAT on DEXA scans. Descriptive statistics were calculated for baseline characteristics. For variables that were normally distributed, the mean ± SD was reported. For dichotomous variables, the number (percent) of patients was listed relative to the total number of patients for whom information was available about the abdominal adiposity.

Changes in WC, VAT, SAT, and VAT/SAT rate were stated as descriptive statistics with comparisons from baseline values by t tests or Wilcoxon signed-rank sum tests, as appropriate. Exploratory multivariate analyses were performed by multiple linear regressions, with as explanatory variables all variables with a p value in univariate analysis < 0.10.

The analyses were performed using SAS version 9.1.

RESULTS

Baseline characteristics. The demographic, clinical, and biological characteristics of the 85 patients are listed in Table 1. The mean age was 39.3 ± 11.4 years (75.9% males). In this population, 22 (25.9%) were overweight, 12 (14.1%) were obese, and 5 (5.9%) were underweight.

Fifty-six patients received 3 or 5 mg/kg infusion of IFX at weeks 0, 2, 6, and thereafter infusions at 6 or 8-week intervals, and 29 patients received etanercept (25 mg twice a week).

The body composition measurements are listed in Table 2. The efficacy of the anti-TNF therapy on clinical symptoms, BASDAI, and biological measures of inflammation was previously described[4].

Effects on body weight and body composition. Compared to baseline, there was a significant increase in BMI after 1 year (0.9 ± 1.4 kg/cm^2, $p < 0.001$) and after 2 years (0.7 ± 1.8 kg/cm^2, $p < 0.05$).

There was a significant increase in WC after 6 months

Table 1. Baseline characteristics of patients with SpA (n = 85). Data are n (%) unless otherwise indicated.

Age, yrs, mean ± SD	39.3 ± 11.4
Sex, male	63 (74.1)
Disease duration, yrs, mean ± SD	13.1 ± 9.5
HLA-B27	75 (88.2)
Patients with axial disease	79 (92.9)
Patients with peripheral disease	10 (11.8)
Patients with psoriasis	8 (9.4)
Patients with inflammatory bowel disease	7 (8.2)
BASDAI, mean ± SD	55.0 ± 20.2
BASFI, mean ± SD	50.6 ± 25.7
VAS pain, mean ± SD	64 ± 21
CRP, mg/l, median (range)	19 (11–37)
ESR, mm/h, median (range)	23.5 (15.0–31.5)
Current use of corticosteroids	12 (14.1)

VAS: visual analog scale; SpA: spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 2. Baseline body composition and abdominal adiposity measurements in patients with SpA (n = 85). Data are mean ± SD unless otherwise indicated.

WC, cm	92.4 ± 13.8
BMI, kg/m^2	24.3 ± 5.0
BMI < 19, n (%)	5 (6.02)
BMI between 19–24, n (%)	44 (53.0)
BMI between 25–29, n (%)	22 (26.5)
BMI ≥ 30, n (%)	12 (14.5)
Total body weight, kg	68.7 ± 13.6
Lean mass, kg	10.0 ± 1.7
Fat mass, kg	4.9 ± 2.2
VAT area, cm^2	112.4 ± 73.2
SAT area, cm^2	211.5 ± 120.6
VAT/SAT	0.58 ± 0.23

WC: waist circumference; BMI: body mass index; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; SpA: spondyloarthritis.

(2.2 ± 3.4 cm, 2.5 ± 3.9%; p < 0.0001), 1 year (2.9 ± 4.4 cm, 3.3 ± 4.9%; p < 0.0001), and 2 years (4.1 ± 5.9 cm, 4.6 ± 6.7%; p < 0.0001) without significant changes between 1 and 2 years.

The change in lean mass was not significant at 1 year (0.2 ± 0.8 kg/cm^2, p > 0.5) and 2 years (0.2 ± 0.8 kg/cm^2, p > 0.5). Changes between the first and second year of treatment were not statistically significant (Table 3).

Effects on abdominal adiposity. Interobserver reproducibility between the 2 readers was evaluated by the analysis of VAT on 30 DEXA whole body scans; the ICC was 0.996 (95% CI 0.992-0.998).

There was a significant gain in VAT after 6 months (13.7 ± 20.6 cm^2, 13.2 ± 20.5%; p < 0.0001), 1 year (21.0 ± 26.6 cm^2, 22.2 ± 28.2%; p < 0.0001), and 2 years (29.1 ± 33.4 cm^2, 32.4 ± 36.6%; p < 0.0001); and in SAT after 6 months (12.5 ± 27.4 cm^2, 8.7 ± 20.4%; p < 0.0001), 1 year (27.1 ± 38.2 cm^2, 17.9 ± 29.4%; p < 0.0001), and 2 years (31.9 ± 53.2 cm^2, 24.2 ± 38.3%; p < 0.0001; Figure 2).

Compared to 6 months, there was a significant increase in VAT and SAT after 1 year (8.3 ± 17.5 cm, 14.1 ± 24.9 cm respectively; p < 0.05) but not between 1 and 2 years.

VAT/SAT significantly increased after 6 months (0.03 ± 0.06, 4.8 ± 11.5%; p < 0.0001), 1 year (0.02 ± 0.06, 4.5 ± 12.7%; p < 0.0001), and after 2 years (0.03 ± 0.06, 8.0 ± 14.7%; p < 0.0001; Table 3) without significant change between 1 and 2 years.

There was no difference of VAT area, SAT area, and VAT/SAT between men and women. We did not identify any relevant determinants of abdominal adiposity measure changes using multivariate analysis, including age, inflammation, and body composition variables.

VAT changes before and after anti-TNF treatment. Body composition measurements were available before the initiation of anti-TNF therapy in 18 patients (94.4% males, mean age of 37.3 yrs) with a mean interval duration of 8.1 (± 3.55) months. Characteristics of these patients were similar to those of the whole population. VAT and SAT did not significantly change over the followup period without anti-TNF therapy [8.1 months; 16.0 (± 11.0) cm^2, 6.75 (± 21.7%), and 25.7 (± 20.8) cm^2, 10.6 (± 10.4%), respectively]. After the initiation of anti-TNF therapy, the 6-month VAT change was not significantly different from the change before anti-TNF therapy [23.3 (± 22.3) cm^2, 15 (± 23.3%), p = 0.4], and the 12-month VAT increase was significantly higher than the VAT change before the anti-TNF therapy. Comparison of SAT changes before and after 6 and 12 months of anti-TNF therapy were not statistically different.

DISCUSSION

In this open, prospective study of patients with SpA receiving anti-TNF-α therapy (etanercept or IFX) over 2 years, we measured a significant increase in BMI, WC, and fat mass. This is the first study conducted in patients with SpA that shows an early significant increase [VAT (mean +13%), SAT (mean +13%), and VAT/SAT (+5%)] of abdominal obesity measured by DEXA.

Obesity is the major risk factor for insulin resistance, dyslipidemia, diabetes, and coronary heart disease[17,18]. By using the BMI, one must rely on the assumption that adipose tissue is distributed evenly over the body[19], which does not

Table 3. Body composition changes in patients with SpA receiving anti-TNF treatment over 6 months, 1 year, and 2 years.

	Change from Baseline to 6 mos	Change from 6 to 12 mos	Change from 6 to 24 mos	Change from Baseline to 1 yr	Change from Baseline to 2 yrs
Body weight, kg	0.7 ± 1.2	0.2 ± 1.1	0.1 ± 1.2	0.8 ± 1.4	0.9 ± 1.7
BMI, kg/cm^2	0.5 ± 1.1*	0.4 ± 1.0*	0.1 ± 1.4	0.9 ± 1.4**	0.7 ± 1.8*
Fat mass	0.3 ± 0.6*	0.3 ± 0.7*	0.3 ± 0.8*	0.6 ± 0.8**	0.7 ± 1.0**
Lean mass	0.4 ± 0.8*	–0.1 ± 0.6	–0.2 ± 0.6	0.2 ± 0.8	0.2 ± 0.8
WC (cm)	2.2 ± 3.4**	1.2 ± 2.7*	1.0 ± 4.6	2.9 ± 4.4**	4.1 ± 5.9**
VAT area, cm^2	13.7 ± 20.6**	8.3 ± 17.5*	11.2 ± 27.0*	21.0 ± 26.6**	29.1 ± 33.4**
SAT area, cm^2	12.5 ± 27.4*	14.1 ± 24.9*	14.2 ± 40.4*	27.1 ± 38.2**	1.9 ± 53.2**
VAT/SAT	0.03 ± 0.06*	0.00 ± 0.04	0.01 ± 0.06	0.02 ± 0.06*	0.03 ± 0.06*

* p < 0.05 ; ** p < 0.001. WC: waist circumference; BMI: body mass index; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; SpA: spondyloarthritis; TNF: tumor necrosis factor.

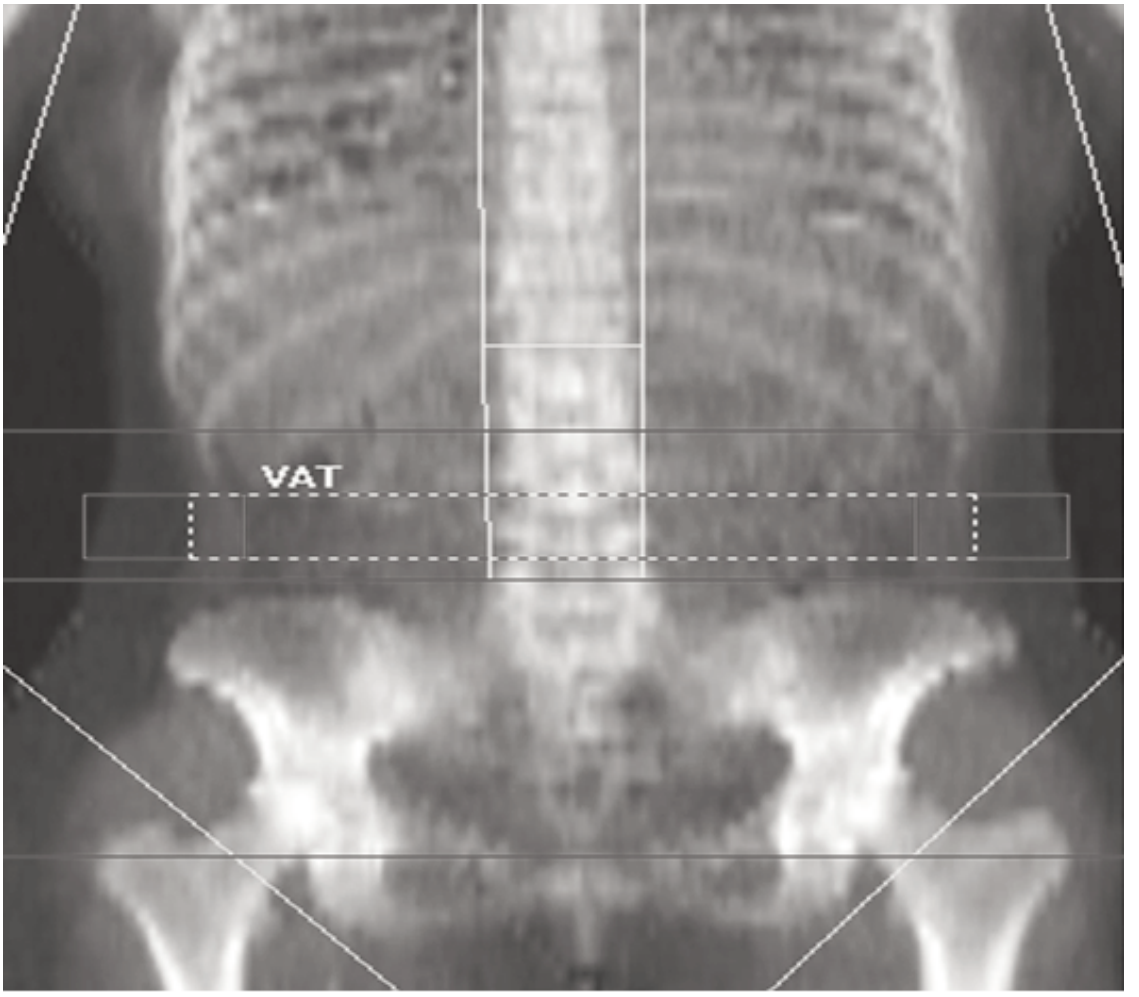

Figure 1. Visceral adipose tissue (VAT) was calculated in a region of interest (ROI) of 5 cm height at the level of the L4 vertebra. This ROI is placed automatically by the software at a fixed distance from the iliac crests, as defined by the operator. The global ROI (large rectangle) is then divided into 3 rectangles, with the right and left heights limiting the skin, the outer muscle edges, and the inner muscle edges, respectively.

take into account the heterogeneity of regional body fat deposition[20]. It is now recognized that the distribution of body fat is more important in this regard than simply the amount of fat.

The use of WC alone has long been considered the best anthropometric measure correlated to the amount of VAT[21]. However, it cannot discriminate subcutaneous from visceral adiposity[22]. It is relevant to assess these 2 components of abdominal adiposity, because studies suggest that only visceral adiposity is highly associated with insulin resistance and CVD[5,6]. VAT is now recognized as a risk factor for the metabolic syndrome, diabetes, and CVD[18,23,24]. Indeed, visceral obesity itself is an independent component of metabolic syndrome[25]; it increases susceptibility to ischemic heart disease and arterial hypertension[26].

Such an assessment is relevant in patients with SpA because a higher prevalence of metabolic syndrome has been reported in this population[27]. CV risk factors [such as higher systolic blood pressure, lower level of high-density lipoprotein (HDL) cholesterol, lower ratio of triglyceride to HDL cholesterol, and higher level of low-density lipoprotein cholesterol] have been shown to be more frequent in patients with SpA than in controls[27].

This is the first study, to our knowledge, to use DEXA to measure abdominal adiposity in patients with SpA. DEXA is a validated technique able to accurately determine cross-sectionally the mass of discrete fat deposits. It is less expensive than CT and MRI, and exposes subjects to smaller doses of radiation than CT[28]. Comparison of VAT results obtained through DEXA whole-body scans, abdominal CT scans, and MRI revealed a good correlation and good accuracy[11]. A DEXA result is more correlated with visceral fat measured by CT than with WC[10].

The fat tissue gain we observed in patients with SpA receiving anti-TNF treatment may be a direct effect of anti-TNF therapy, an indirect one through the effect on

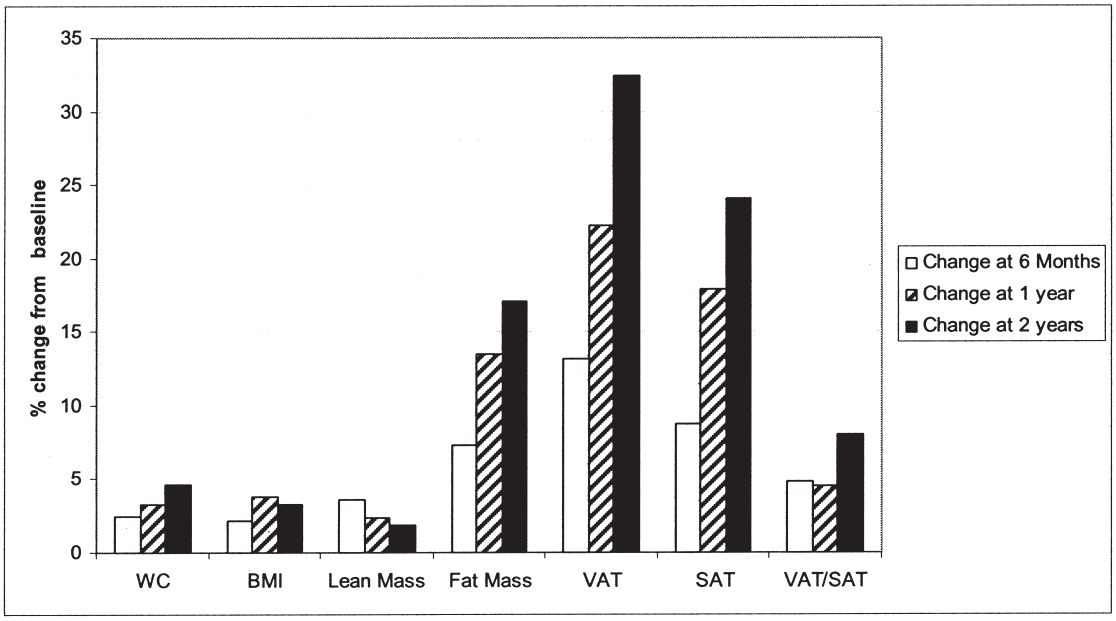

Figure 2. Relative changes (percent) in the WC, BMI, and abdominal body composition (lean and fat mass) and adiposity (VAT, SAT, and VAT/SAT) compared to baseline. BMI: body mass index; WC: waist circumference; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue.

inflammation, or both. TNF-α plays an important role in the development of cachexia in chronic diseases: reducing gastric emptying and peristalsis[29], inducing lipolysis, inhibiting lipid synthesis[30], and increasing proteolysis[31]. In 20 patients with active Crohn disease, 1 injection of IFX was associated with an increase in body weight as early as 4 weeks after the injection[32], suggesting a direct relationship with inflammation control. In 40 patients with early rheumatoid arthritis and failure of methotrexate treatment, similar reduction of disease activity was observed in a group receiving IFX and another group receiving a combination of DMARD, but only the former group had an increase in fat mass, suggesting a drug-specific effect of the anti-TNF therapy. The effects of anti-TNF treatment on weight and body composition can be mediated by improvements in well-being and increase in appetite through control of disease activity, if these phenomena occur early after the introduction of treatment. Another hypothesis is that physical activity may not improve in the first months despite the efficacy of treatment, explaining the different changes of lean and fat masses. A previous study showed that patients with SpA who were overweight had a greater burden of symptoms, worse perceptions regarding the benefits of exercise, and enhanced awareness of their barriers to exercising[33].

Our study has limitations. It is an open-design study with a small sample size. We did not study the associated risk factors for CVD, including physical activity and nutrition, and thus we cannot draw conclusions based on the relevance of the measured changes, especially the consequences of the increase of the visceral fat on the CV risk. Our study was uncontrolled and could not differentiate between a specific effect of TNF antagonists and a general effect of reduced inflammatory activity. One of the best ways to assess whether the initiation of anti-TNF therapy is truly responsible for the weight, body composition, and VAT changes would have been to have the measures of an equivalent time period of followup before the anti-TNF treatment for all the patients. Data in 18 patients showed that VAT and SAT change did not significantly change over the followup period before the anti-TNF therapy. The magnitude of the changes was similar to those observed 6 months after the initiation of anti-TNF treatment for SAT and VAT and lower than the 12-month VAT increase. However, we cannot draw conclusions because of the limited number of patients.

Patients with SpA who are receiving anti-TNF-α therapy have significant changes of abdominal obesity after 1 and 2 years of treatment measured by DEXA. Prospective studies are required to confirm these data and to investigate the relationship between these changes and CV risk.

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Early Increase of Abdominal Adiposity in Patients with Spondyloarthritis Receiving Anti-tumor Necrosis Factor-α Treatment

Hmamouchi I, Roux C, Paternotte S, Kolta S, Dougados M, Briot K. Early increase of abdominal adiposity in patients with spondyloarthritis receiving anti-tumor necrosis factor-α treatment. J Rheumatol 2014;41:1112–7. In the Materials and Methods section, paragraph 4, the device used for the study was given incorrectly. The correct device was a Delphi W (Hologic). We regret the error.

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