Color and Duplex Doppler Sonography to Detect Sacroiliitis and Spinal Inflammation in Ankylosing Spondylitis. Can This Method Reveal Response to Anti-Tumor Necrosis Factor Therapy?

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ABSTRACT. ***Objective.*** To investigate the role of color and duplex Doppler ultrasound (CDDUS) in the detection of sacroiliac (SI) and spinal inflammation, as well as response to anti-tumor necrosis factor (TNF) therapy in patients with ankylosing spondylitis (AS).

Methods. We included 39 consecutive patients with AS followed at our center and 14 healthy controls. In the AS and control groups, blood vessels in SI joints and lumbar vertebral (LV) and thoracal vertebral (TV) paraspinal areas were investigated by CDDUS. When the artery was found, the resistive index (RI) was measured by CDDUS. Disease activity characteristics (ESR, CRP, BASDAI, and BASMI) were evaluated in patients with AS. In 11 patients for whom anti-TNF therapy was indicated, CDDUS measurements were performed before and on Week 12 of therapy.

Results. In patients with AS, RI values of SI joints and of LV and TV areas were lower than in controls (all $p \leq 0.01$). In AS patients with active disease according to BASDAI, RI values of TV ($p = 0.0013$) and LV ($p = 0.027$) were significantly lower than in the inactive group. In the group with active AS, SI RI was nonsignificantly lower ($p = 0.16$). After anti-TNF therapy, there were significant increases in mean SI RI ($p = 0.028$) and LV RI ($p = 0.039$), and a nonsignificant increase in TV RI ($p > 0.05$).

Conclusion. CDDUS may be an alternative, less expensive, and easier method for detecting inflammation secondary to increased SI and spinal vascularization and in evaluating response to anti-TNF therapy in AS. (J Rheumatol 2007;34:110–6)

Key Indexing Terms:
COLOR AND DUPLEX DOPPLER ULTRASONOGRAPHY
ANKYLOSING SPONDYLITIS
TUMOR NECROSIS FACTOR INHIBITOR
SACROILIITIS

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily involves the axial skeleton. The current standard imaging method in AS is sacroiliac (SI) and spinal conventional plain radiography. Radiography reveals the consequences of inflammation, but cannot detect active inflammatory lesions when used alone[1]. Magnetic resonance imaging (MRI), on the other hand, can detect SI and spinal active inflammatory lesions[2].

The introduction of anti-tumor necrosis factor (TNF) drugs for treatment of AS has led to effective treatment of disease symptoms and signs[1-4]. However, the effect of these costly drugs on structural damage in addition to the clinical findings is not clear[5]. MRI can quantify active spinal inflammatory lesions over short periods of time in patients with active AS treated with anti-TNF drugs[2]. Nevertheless, MRI is a relatively expensive and time-consuming method, and its routine use in every patient receiving TNF therapy would be difficult in daily practice. Another factor that limits usage of MRI is that an important proportion of AS patients have prostheses. Therefore, an easier and cheaper method is needed to detect the degree of spinal inflammation.

Musculoskeletal ultrasonography (US) has gained increasing attention in many areas of rheumatology[6]. In the area of spondyloarthropathy, Doppler US has been used frequently to assess enthesitis[7]. It was demonstrated that signs of active sacroiliitis could be detected by the color and duplex Doppler ultrasonographic (CDDUS) method, and that antiinflammatory therapy would lead to improvement in signs of active sacroiliitis in addition to clinical recovery[8]. In another recent study, contrast-enhanced color Doppler ultrasound and MRI were compared as to their value to diagnose SI inflammation, and it was shown that ultrasound had a high negative predictive value in the detection of inflamed SI joints[9]. In our study, we determined the degree of SI and spinal inflammation in AS patients by CDDUS, evaluated their relationship with clinical activity variables, and sought to detect changes following anti-TNF therapy.

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MATERIALS AND METHODS

Our study included 39 consecutive patients with AS (24 men, 15 women, mean age 37.3 ± 10.8 yrs) being followed at the Rheumatology Department, Trakya University Medical Faculty, and 14 age and sex-matched controls (8 men, 6 women, mean age 37.2 ± 10.7 yrs). All patients and controls underwent CDDUS of bilateral SI joints, and of lumbar vertebral (LV) and thoracal vertebral (TV) paraspinal areas. All patients with AS fulfilled the modified New York classification criteria for AS[10]. All patient demographic and clinical data and drug history were recorded from medical charts. The study was approved by the institutional ethical committee of our faculty. All patients were given detailed information about the aim of the study and all gave written informed consent for participation.

In patients with AS, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were determined and physical examination was performed; Bath AS Disease Activity Index (BASDAI) and Bath AS Functional Index (BASFI) scores were calculated using visual analog scales. In addition, chest expansion, finger-to-floor distance, occiput-to-wall distance, tragus-to-wall distance, modified Schober (mSchober), lateral spinal flexion, cervical rotation, and intermalleolar distance were measured; and Bath AS Metrology Index (BASMI) was calculated using cervical rotation, tragus-to-wall distance, lateral spinal flexion, mSchober, and intermalleolar distance[11].

Conventional radiographs of the pelvis and lumbar spine were available in all patients. Chronic changes in one SI joint were scored between 0 and 4 on the basis of the modified New York criteria[10]; and the total chronicity score for both SI joints varied between 0 and 8. The Bath AS Radiology Index (BASRI) was used to score hip joints and lumbar spinal radiography. As we did not evaluate cervical vertebrae in our study, we did not include them into the BASRI score. Scoring of SI joints and vertebrae was performed by one of the authors (EU).

CDDUS analysis. When performing CDDUS (Sonoline Elegra, Siemens Medical Systems Inc., Issaquah, WA, USA), a 7.5-MHz, high-resolution linear transducer was used in subjects with a skin-subcutaneous fat tissue thickness < 3 cm, and a 3.5 MHz, high-resolution convex transducer was used in subjects with skin-subcutaneous fat tissue thickness > 3 cm. For CDDUS, the color box was focused on the area being examined. Standardized machine settings that were applied included color Doppler gain 60–120 dB, wall filter 51–65 Hz, and pulse repetition frequency 300–850 Hz.

The CDDUS method for examination of midlumbar and lower thoracal paraspinal areas was modified from the study of Arslan, *et al*[8], which used this method for examination of SI joints. Subjects were in the prone position during examination. In order to detect SI joints, the transducer was moved in a transverse direction 3–4 cm to the right and left of the sacral spinous processes in the gray-scale US mode; measurements were performed from the posterior point of the cleft-shaped SI joint that was closest to the transducer (Figure 1). If possible, care was taken to perform the measurement from the arterial structure within the SI joint. When no arterial recording could be obtained from inside the joint, measurements were taken from the arterial structure closest to the joint. In LV and TV areas, CDDUS measurements were performed in transverse or sagittal oblique view, from the muscular branches of the intercostal or lumbar arteries closest to the vertebral body in the right or left paraspinal areas (Figure 2). Resistive index (RI) [peak systolic velocity – end-diastolic velocity / peak systolic velocity] values obtained from CDDUS performed in SI and paraspinal areas were calculated by the program loaded on the machine. Measurements in each examination area were repeated 3 times, mean values of those measurements were used for evaluation, and the results were recorded. In each case CDDUS was completed in about 25–30 minutes. All patients were evaluated by one radiologist experienced in CDDUS who was unaware of the subjects' clinical and laboratory data. To prevent variability in measurements, examination in all subjects was performed by the same radiologist. The reproducibility of the CDDUS measurement was evaluated in 10 subjects within 1 week of the first examination. Intraobserver variability correlation coefficient values for SI, TV, and LV RI were 0.845, 0.821, and 0.805, respectively.

In addition, 11 patients with AS (7 men, 4 women, mean age 38.2 yrs; mean disease duration 11.2 yrs) were administered anti-TNF therapy within the study period. Infliximab was administered in 7 patients (dosage 5 mg/kg IV initially and at 2nd, 6th, and 12th weeks), and etanercept in 4 patients (2 × 25 mg/week SC). Disease activity evaluation and CDDUS measurements were repeated before therapy and on the 12th week of therapy.

Chi-square test for comparison of categoric variables and paired and unpaired t tests for continuous variables were applied. Correlations at a group level were expressed as Pearson's correlation.

RESULTS

CDDUS detected arterial vascularity for measurement within or around SI joints and in paraspinal areas in all AS patients

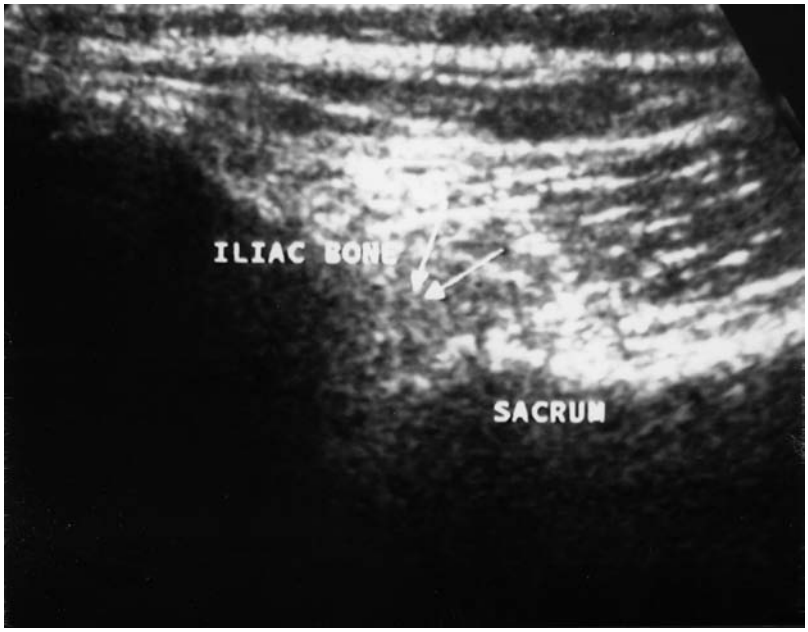

Figure 1. A gray-scale sonogram obtained in prone position shows a hypoechogenic area in the form of a cleft that belongs to the posterior part of the right SI joint (arrows).

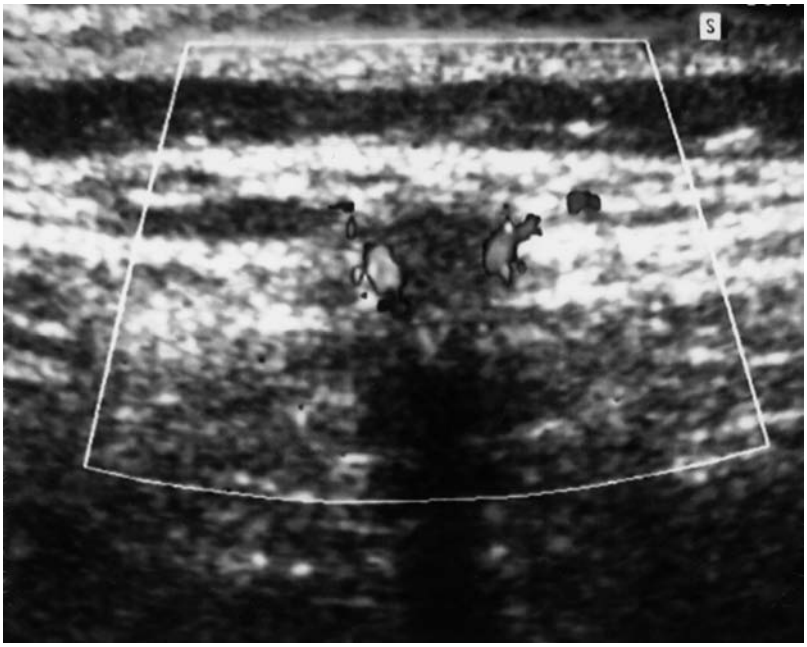

Figure 2. Dense posterior shadowing of vertebrae and arterial vascular structures examined in paraspinal area seen on CDDUS image.

and in controls. The demographic and clinical features of patients and controls are shown in Table 1. In the AS group, mean RI values of SI joints, LV, and TV areas were significantly lower than in controls (p = 0.003, 0.004, and 0.01, respectively).

In patients with AS who had active disease according to BASDAI score, the ratio of men was higher (p = 0.034), and higher values were recorded for mean ESR (p = 0.05) and CRP (p < 0.001). Subjects with active AS tended to have longer finger-to-floor distance (p = 0.05) and morning stiffness (p = 0.06), and less chest expansion (p = 0.08). Mean BASFI score in AS patients with active disease was higher than in patients with inactive disease (p = 0.003). Although mean SI RI in the active group tended to be lower, this difference was not significant (p = 0.16). Mean LV and TV RI values were significantly higher in the active group (p = 0.0013 and 0.027, respectively). The comparison of various features between active and inactive AS patients is seen in Table 2.

In the control group, TV RI level was correlated to LV RI (r = 0.63, p = 0.021) and SI RI (r = 0.67, p = 0.012) levels. In the AS group, TV RI levels were correlated to LV RI levels (r = 0.39, p = 0.017). In addition, TV RI level was positively correlated to mean mSchober (r = 0.43, p = 0.007), cervical rotation (r = 0.35, p = 0.032), and chest expansion (r = 0.32, p = 0.049); and negatively correlated with finger-to-floor distance (r = –0.33, p = 0.04), BASMI score (r = –0.32, p = 0.049), and BASRI lumbar score (r = -0.34, p = 0.037).

Table 1. The demographic and general clinical features of patients with AS and controls.

	AS, N = 39	Control, N = 14	p
M/F	24/15	8/6	NS
Age, mean ± SD yrs	37.3 ± 10.8	37.2 ± 10.7	NS
Sulfasalazine usage, n (%)	17 (43.6)	—	—
Methotrexate usage, n (%)	4 (10.3)	—	—
NSAID usage, n (%)	28 (71.8)	—	—
Hip prosthesis, n (%)	6 (16.6)	—	—
History of uveitis, n (%)	5 (13.2)	—	—
Mean sacroiliac RI	0.820 ± 0.06	0.881 ± 0.05	0.003
Thoracal vertebrae RI	0.818 ± 0.04	0.857 ± 0.04	0.004
Lumbar vertebrae RI	0.847 ± 0.04	0.885 ± 0.03	0.01

NSAID: Nonsteroidal antiinflammatory drugs; RI: resistive index.

Table 2. Characteristics of patients evaluated in the study according to their status of active or inactive disease based on BASDAI score (> 4 vs ≤ 4, respectively).

	Active AS, N = 13	Inactive AS N = 28	p
M/F	11/2	14/14	0.034
Age, mean ± SD yrs	34.7 ± 10.9	38.4 ± 10.4	NS
Duration of disease, yrs	10.9 ± 6.4	11.1 ± 9.2	NS
ESR, mm/h	46.7 ± 23.4	30.2 ± 26.2	0.05
CRP, mg/dl	4.55 ± 2.6	1.76 ± 1.7	< 0.001
Morning stiffness, min	36.4 ± 17.4	25.4 ± 18	0.06
Chest expansion, cm	2.1 ± 1.45	2.9 ± 1.35	0.08
Finger-to-floor distance, cm	23.8 ± 12.5	14 ± 16.1	0.05
Occiput-to-wall distance, cm	8.4 ± 10.8	5.3 ± 9.5	NS
Modified Schober, cm	2.3 ± 1.8	3.1 ± 1.5	NS
Lateral spinal flexion, cm	9.6 ± 6	10.1 ± 5.8	NS
Cervical rotation, degrees	97.1 ± 46.9	103.7 ± 43.9	NS
Intermalleolar distance, cm	96.6 ± 28.3	93.7 ± 21.5	NS
BASMI	4.36 ± 2.9	3.63 ± 3.2	NS
BASFI	4.7 ± 2.4	2.3 ± 2.2	0.003
SI joint radiography, total score	7.3 ± 0.98	6.8 ± 1.3	NS
BASRI hips	2.6 ± 1.3	2.03 ± 1.5	NS
BASRI lumbar	2.67 ± 0.9	2.03 ± 1.4	NS
Mean sacroiliac RI	0.797 ± 0.08	0.828 ± 0.06	NS
Thoracal vertebrae RI	0.789 ± 0.03	0.825 ± 0.03	0.013
Lumbar vertebrae RI	0.820 ± 0.06	0.863 ± 0.03	0.027

ESR: erythrocyte sedimentation rate; C-reactive protein; BASMI: Bath AS Mobility Index; BASFI: Bath AS Functional Index; BASRI: Bath AS Radiology Index; SI: sacroiliac; RI: resistive index; NS: not significant.

When AS patients with a total BASRI score ≥ 5 were compared with others, the group with the high BASRI score was observed to have a significantly higher SI RI value (0.847 ± 0.03 vs 0.798 ± 0.07; p = 0.017), and a nonsignificantly lower TV RI value (0.807 ± 0.03 vs 0.830 ± 0.04; p = 0.09).

There were significant increases in mean SI (p = 0.013) and LV RI (p = 0.005) levels in patients with AS after administration of anti-TNF; however, there was no significant change in TV RI (p = 0.1) (Figures 3 and 4). RI values before and after 12 weeks of therapy in AS patients receiving anti-TNF are shown in Table 3.

DISCUSSION

In our study, AS patients had significantly lower RI values of SI joints and of LV and TV areas when compared to controls. It was suggested that proangiogenic factors lead to increased vascularization in regions of prominent inflammation such as SI joints, which could be associated with disease activity in patients with AS[12,13]. As a result, RI value is expected to be lower in patients with active inflammation because of hypervascularization[8,14].

In the CDDUS study by Arslan, *et al*[8], RI was similarly significantly decreased in patients with active sacroiliitis, and then increased after antiinflammatory therapy. However, the study group was heterogenous: patients with tuberculosis and psoriatic arthritis were included. In addition, data in that study were not compared with clinical disease activity characteristics. Anti-TNF agents were not administered as therapies. Our study was superior to the Arslan study in that our study group was homogenous, including only patients with AS. Second, we compared CDDUS RI values with clinical activity variables such as the BASDAI, BASMI, and BASFI. In addition, our study is the first to evaluate the effects of anti-TNF drugs on CDDUS.

Recently, Klauser, *et al*[9] reported that, compared with MRI, microbubble contrast-enhanced color Doppler US was a sensitive technique with high negative predictive value for detection of active sacroiliitis. However, their study considered vascularization within the SI joints but not in the areas around the joints. In the study of Arslan, *et al*[8] and in our study, vascularization around SI joints was examined and measurements were made in all patients. Moreover, the purpose of the study by Klauser, *et al*[9] was to test the diagnostic usefulness of Doppler US in inflammatory back pain. Their study group was not as homogenous as ours: it included 103 patients with inflammatory back pain, 75% of whom turned out to have some form of spondyloarthropathy. The study was also different in that it did not include data such as clinical activity parameters and changes after anti-TNF therapy. Neither of the 2 studies evaluated LV and TV. Ours was the first study to evaluate LV and TV by CDDUS.

In our patients with active AS according to BASDAI, the LV and TV RI values were lower. The mean RI tended to be lower around the SI joints in the active group; however, the

difference was not significant. As a result, we might suggest that CDDUS examination may show disease activity better in LV and TV than in SI joints. The mean disease duration in our AS patients was nearly 10 years. Therefore, the difference in spinal inflammation between active and inactive groups was prominent; however, the difference in the degree of inflammation of SI joints between active and inactive groups became less significant because of the long disease duration of our AS patients.

It was observed that radiologic score in AS patients was correlated to spinal mobility as evaluated by BASMI[15]. In our study, TV RI level was negatively correlated to BASMI score. BASRI lumbar score, which was used as the radiographic score in our study, was negatively correlated to TV RI value. In addition, it was observed that in the group with higher total BASRI score who had more prominent SI and spinal radiographic findings, SI RI values were not indicative of increased vascularization. Nevertheless, TV RI values were

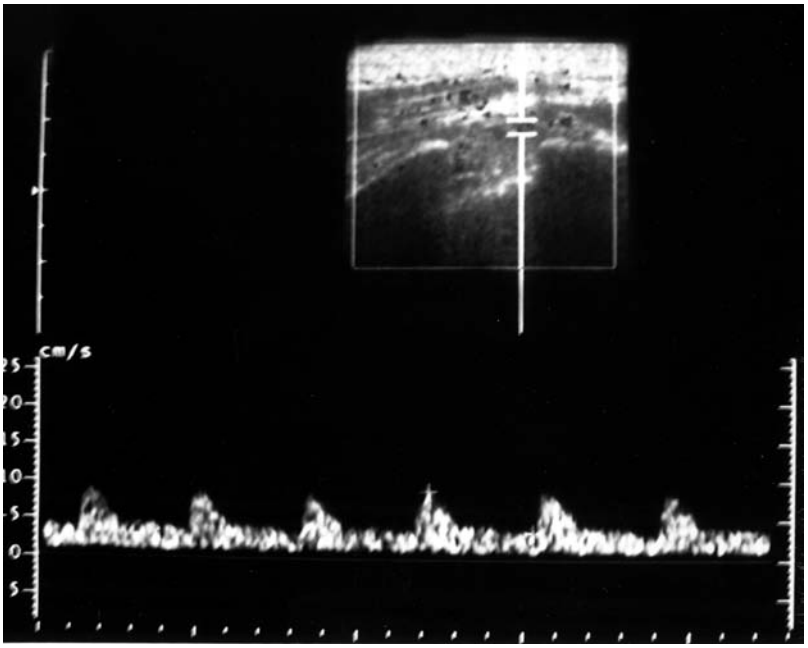

Figure 3. Low-resistance flow pattern compatible with acute inflammation obtained in spectral Doppler analysis of the right SI joint of one patient with active sacroiliitis.

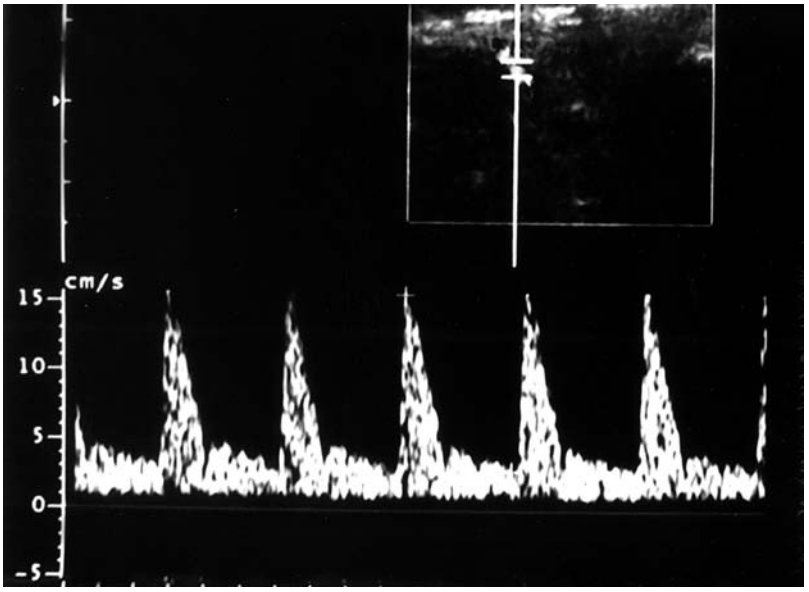

Figure 4. Doppler spectrum of the same joint in the same patient shown in Figure 3 after 12 weeks of anti-TNF therapy shows a high resistive index flow pattern reflecting regression of inflammation.

Table 3. Disease activity and Doppler ultrasound characteristics before and after tumor necrosis factor-α (TNF-α) therapy.

	Before TNF-α	After TNF-α	p
ESR, mm/h	61.9 ± 23.4	10.6 ± 5.6	< 0.001
CRP, mg/dl	5.5 ± 2.9	0.63 ± 0.3	0.001
Morning stiffness, min	32.5 ± 19.3	3.1 ± 3.6	0.001
Chest expansion, cm	1.95 ± 1.5	2.27 ± 1.2	NS
Finger-to-floor distance, cm	21.4 ± 15.6	16.1 ± 13.2	0.016
Occiput-to-wall distance, cm	5.9 ± 7	5.2 ± 6.9	NS
Modified Schober, cm	2.54 ± 1.8	3.1 ± 2.1	0.1
Lateral spinal flexion, cm	8 ± 4.1	10.9 ± 5.3	0.003
Cervical rotation, degrees	95.5 ± 39.4	110 ± 34.1	0.007
Intermalleolar distance, cm	82.5 ± 22.6	95.8 ± 20	0.001
BASMI	4.45 ± 2.6	3.36 ± 2.9	0.006
BASFI	4.29 ± 2.6	1.55 ± 1.5	< 0.001
BASDAI	5.37 ± 1.5	1.56 ± 1.1	< 0.001
Mean sacroiliac RI	0.814 ± 0.07	0.884 ± 0.03	0.013
Thoracal vertebrae RI	0.812 ± 0.05	0.855 ± 0.05	0.1
Lumbar vertebrae RI	0.821 ± 0.06	0.883 ± 0.04	0.005

For definitions see Table 2.

associated with increased vascularization. This suggests that there is regression of SI inflammation in patients with advanced radiographic features and that findings of spinal inflammation are more prominent.

SI and LV RI levels in our AS patients improved significantly after anti-TNF therapy. Although TV RI showed improvement, the difference was not significant. In various studies, it was demonstrated that anti-TNF therapy led to regression of SI and spinal inflammation findings on MRI[1,2]. Conventional radiography might show chronic spinal changes; however, it does not give immediate information about response to therapy. Thus radiography might help only in longterm followup. In the study by Arslan, *et al*[8], it was demonstrated that SI joint RI increased after antiinflammatory therapy and reached levels similar to those in the control group. Thus, CDDUS was shown to be useful to demonstrate degree of SI and spinal inflammation as well as regression of inflammatory signs after anti-TNF therapy.

As limitations of our study we note that evaluations were performed by only one radiologist, and no comparison with a more standard method like MRI was made. In addition, it was a disadvantage that no previous data were available on vascularization around LV and TV regions. However, RI values in these areas were lower in patients than in controls and in the active group versus the inactive group; moreover, there was a significant increase in LV RI after anti-TNF therapy. Together, these findings prove that our methods were correct. Another limitation of our study was that the control group and the treatment group were small. Although statistically significant, we do not know the clinical significance of the differences in RI between AS patients and controls. This should be clarified in future studies.

In conclusion, the CDDUS method might be useful to detect degree of inflammation in SI joints and in LV and TV paraspinal areas in patients with AS. In patients with active disease, a low RI may indicate increased inflammation. When evaluating early response to anti-TNF therapy in patients with active disease, CDDUS might be an alternative to MRI because it is inexpensive, easy, can be performed at the bedside, and is less time-consuming. Therefore, as stated in other studies, results of CDDUS in patients with inactive disease were nearly similar to controls. Thus, rather than as a method used for diagnosis, CDDUS might be more suitable to detect disease activity and to obtain more quantitative data about response to therapy. Ours is the first study using CDDUS to evaluate LV and TV vascularization and to interpret response to anti-TNF therapy in light of clinical characteristics. This method merits further study to develop and standardize this use of CDDUS.

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