ORIGINAL RESEARCH

Spectral Doppler and automated software-guided ultrasound assessment of bilateral common carotid intima-media thickness in spondyloarthritis: is there a correlation with clinical findings?

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Abstract

**Background and aim:** Limited information is currently available about whether carotid intima-media thickness (IMT) correlates with the degree of disease activity in spondyloarthritis. The objective of this study was to evaluate the correlation between articular and carotid ultrasound data and laboratory and clinical variables in patients with spondyloarthritis.

**Methods:** Twenty-two patients with spondyloarthritis, recruited consecutively via the spondyloarthritis service of the Universidade Pontificia Católica de Campinas, São Paulo, Brazil, were assessed using carotid artery ultrasound (radiofrequency quality intima-media thickness, RF-QIMT), joint ultrasound, clinical evaluation, and laboratory tests.

**Results:** Mean (standard deviation, SD) carotid RF-QIMT was 0.643 (0.16) mm. Mean (SD) resistive index (RI) values for the right and left carotid arteries were 0.67 (0.12) and 0.82 (0.38), respectively. Mean (SD) RI values for the right and left sacroiliac joints were 1.10 (0.97) and 0.94 (0.13), respectively.

Several significant correlations were detected between ultrasound, clinical, and laboratory variables. Notably, there were correlations between sacroiliac RI and erythrocyte sedimentation rate ($p=0.027$) and RF-QIMT ($p=0.037$); between RF-QIMT and Framingham score ($p=0.012$) and metabolic parameters, including abdominal waist measurement, body mass index (BMI) ($p=0.032$ to $p=0.044$).

**Conclusions:** In patients with spondyloarthritis, RF-QIMT detected atherosclerotic changes in the carotid artery wall, and spectral Doppler detected inflammatory activity in sacroiliac joints. Positive correlations were observed between these ultrasound findings and parameters reflecting patients’ metabolic profile and alterations in inflammatory markers.

**Keywords:** atherosclerosis, carotid artery, inflammation, sacroiliac joint, spectral Doppler, spondyloarthritis, ultrasonography.

Citation

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Introduction

The spondyloarthritides are rheumatologic inflammatory diseases of the axial skeleton. A key feature of these disorders is sacroilitis, which may be one-sided or bilateral. Patients with seronegative ankylosing spondylitis show an abnormal increase in vascularization within the sacroiliac joint, which can be observed using ultrasound, with a decrease in the internal resistive index (RI) of the blood vessels, providing a quantitative indication that the disease is in its active phase.1 A study involving patients with ankylosing spondylitis demonstrated blood flow with an average RI of 0.56 among 205 sacroiliac joints, which corresponded to 90.7% of sacroiliitis detected by spectral Doppler and 37 (38.5%) sacroiliac joints with subclinical inflammatory activity.2 In another study, the average RI was 0.97 in a control group of healthy individuals, compared to 0.53 in...
patients with ankylosing spondylitis, illustrating the correlation between reduced RI and increased inflammatory activity in the disease, which has also been demonstrated in other studies.1,2,4–6

Nowadays, nuclear magnetic resonance imaging (MRI) is used frequently for the radiologic diagnosis of this disease and to detect early regressive lesions, with X-ray used for later lesions. However, ultrasound is used widely within the rheumatology field to detect articular inflammatory alterations.7,8

In addition to joint inflammation, patients with spondyloarthritis experience systemic inflammation, including atherosclerosis.9 They have an increased risk of cardiovascular events10 and can develop inflammation of large blood vessels, including the aorta.11 Increased carotid intima-media thickness (IMT) is a common marker of atherosclerotic involvement of the vascular structure, thereby indicating coronary artery disease, cerebrovascular disease, and peripheral arterial disease. Carotid IMT has received increasing attention due to its role as an independent prognostic factor for chronic kidney disease, diabetes, hypertension, and systemic inflammatory diseases such as systemic lupus erythematosus, Behçet’s disease, and psoriasis.12,13 Indeed, several studies have found that carotid IMT is increased in patients with spondyloarthritis even in the absence of classical cardiovascular risk factors.9,14,15 However, little information is currently available about whether carotid IMT correlates with the degree of disease activity in spondyloarthritis, though one small study did find a positive correlation.14 The objective of the current study was to evaluate correlations between articular and carotid ultrasound data and laboratory and clinical variables in patients with spondyloarthritis. To the best of our knowledge, the current study is the first to evaluate new ultrasonographic variables including an evaluation of automated measurement of the medial and intimal layer by radiofrequency and the correlation with other variables such as sacroiliac and carotid RI.

Methods

Patients and study design

The study enrolled consecutive patients from the rheumatology outpatient clinic who had spondyloarthritis, which was classified using the Assessment of SpondyloArthritis international Society (ASAS) criteria for axial spondyloarthritis. In addition to meeting ASAS criteria, patients had to have low density lipoprotein cholesterol (LDL) levels below 130 mg/dL, in line with the Modified National Cholesterol Education Program (2004) guidelines.16,17 Patients with other inflammatory pathologies or hypothyroidism were excluded from the study. Patients were evaluated at the PUC-Campinas Ambulatory Rheumatology Center. Ethical approval was obtained for the study protocol, and all patients provided written informed consent. Patients underwent clinical assessment of their spondyloarthritis, laboratory parameters reflecting their metabolic profile, and their cardiovascular risk. They also underwent ultrasound evaluation of the sacroiliac joints, common carotid artery, and calcaneus (Achilles tendon).

Clinical assessments

Disease functionality was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI) and disease activity using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the ankylosing spondylitis activity score (ASDAS).17,18

Laboratory tests included measurement of the erythrocyte sedimentation rate (ESR), C-reactive protein level, lipid profile (including total cholesterol, LDL, high density lipoprotein cholesterol [HDL] and triglycerides), fasting glucose level, and uric acid level. In addition, homocysteine was measured in some patients. Homocysteine is a sulfur-containing amino acid formed from demethylation of the essential amino acid methionine.19 It is considered a marker of blood vessel injury, which can lead to atherogenesis and thrombosis. The relationship between hyperhomocysteinemia and blood vessel damage was originally proposed in 1969, and since then several studies have shown that it is an independent risk factor for the development of coronary disease.20–22 Due to budget constraints, HLA-B27 testing was not performed.

Patients’ cardiovascular risk was assessed using anthropometric data including abdominal waist measurement and body mass index (BMI) and the Framingham score.

Ultrasound assessments

Ultrasonography assessments of the common carotid artery, sacral and internal iliac arteries, sacroiliac joint, and Achilles tendon were performed in blinded fashion by a rheumatologist with 9 years of experience in ultrasonography. The ultrasound machine used was an Esaote – MyLab 50 model. The calcaneus and sacroiliac joint assessments used mode B linear probes of frequency 6.0–18 MHz and power Doppler frequency of 6.6–8 MHz with Pulse Repetition Frequency that varied from 0.5 Hz to 1.0 MHz, and low filter. For the carotid assessments, a linear probe with 3.5–10 MHz frequency, Doppler 3.3–5.0 MHz, and average filter were used. The parameters used for carotid and articular spectral RI were based on Doppler frequencies of 3.3 and 8.0 MHz, respectively. The angulation to calculate the common carotid artery RI was less than 60 degrees. IMT and the carotid average IMT were determined using automatic software that assesses radiofrequency quality intima-media thickness (RF-QIMT). This software provides, in real time, a measurement of the average of six mean values obtained during six consecutive cardiac cycles. IMT was measured in the wall of the most distal 15 mm length of the common carotid artery, 10 mm from the distal extremity, just proximal to the bifurcation. According to age-categorized values (based on the standard deviation for a sample population aged ≥25 years), mean RF-QIMT values of between 0.4 and 0.65 mm are considered normal (expected QIMT), between 0.65 and 0.75 mm are abnormal, and between 0.75 and 1.5 mm are very abnormal.23
Bilateral assessments of the sacroiliac joints, Achilles tendons, and carotid arteries were performed. The probe position used to assess the sacroiliac joints was cross-sectional, from the superior iliac crest to the inferior iliac crest (Figure 1). To assess the Achilles tendon, the probe position was longitudinal, in the calcaneal posterior recess. For the evaluation of the common carotid artery, the probe began transversely in the direction of the thyroid gland and was set longitudinally (Figure 2). Measurements in the sacroiliac gray-scale scan were accomplished by tracing a line between the recess of the cortical bones from the iliac and sacral crest and a line to the sacrum area in order to calculate the polygon area. The Achilles tendon assessment was included because structural alterations such as thickening are common in patients with enthesopathy due to spondyloarthritis.²⁴
Ultrasound parameters obtained for this study included carotid RI and sacroiliac RI, carotid RF-QIMT, carotid diameter, sacral area measurement, and Achilles tendon measurement. The presence of carotid plaques was also evaluated.

**Statistical methods**

A descriptive evaluation of the study sample and analysis of parametric and nonparametric variables was performed, with data presented as mean (standard deviation, SD) or percentages. Spearman’s and Pearson’s correlation analyses were performed to identify significant relationships between ultrasound, clinical, and laboratory parameters. Statistical significance was indicated by \( p < 0.05 \). Statistical analysis was performed using SPSS17 software.

**Results**

A total of 22 patients were evaluated, of whom 27.27% had antero-posterior sacroiliac X-ray evidence of spondyloarthritis, of either degree 3 (articular space reduction and sclerosis) or degree 4 (ankylosis), while 72.72% had sacroiliac MRI evidence (based on weighted sequences in T1 and T2 or short-time inversion recovery), with subchondral bone marrow edema. Three patients had psoriatic arthritis as well as axial involvement.

Patients’ demographic and disease characteristics are summarized in Table 1. Most were male (63.6%) and Caucasian (86.4%). The average age of the patients was just over 38 years, and the mean duration of inflammatory back pain was 8 years. Mean (SD) scores for the BASFI, BASDAI and ASDAS were 4.69 (2.30), 4.41 (2.00), and 2.51 (0.68), respectively. The most common treatment being received for spondyloarthritis was anti-tumor necrosis factor therapy (45.45%). Mean values for parameters reflecting patients’ metabolic/cardiovascular profile were generally within the normal range (Table 2).

Parameters derived from ultrasound measurements of the carotid artery, sacroiliac, and Achilles tendon are shown in Table 3. Overall, mean RI values for both sacroiliac joints were above 1.0, whereas mean RI values for the carotid arteries were below 1.0. Only 14 of 44 sacroiliac joints had a low RI (mean RI 0.71). Mean (SD) carotid RF-QIMT, 0.643 (0.16) mm, was higher than the expected age-standardized QIMT, 0.529 (0.10) mm. There was no evidence of carotid plaques.

Significant correlations between parameters are summarized in Table 4. There was no statistically significant correlation between ultrasound parameters and disease activity scores (BASDAI/ASDAS). Correlations were found between sacroiliac RI and ESR and between sacroiliac RI and Framingham score. Expected QIMT (but not RF-QIMT) correlated with Framingham score (Figure 3). There were correlations between sacral area and both sacroiliac RI and carotid RI, and between sacral

| Table 1. Demographics and spondyloarthritis disease characteristics (n=22). |
|-------------------------|-----------------|
| **Parameter**           | **Value, mean (SD) unless indicated otherwise** |
| Sex (male/female), n (%)| 14 (63.6)/8 (36.4) |
| Race, n (%)             |               |
| Caucasian               | 19 (86.36)    |
| African                 | 3 (13.63)     |
| Age (years)             | 38.36 (9.48)  |
| Duration of inflammatory back pain (years) | 8 (7.18) |
| BASFI score             | 4.69 (2.30)   |
| BASDAI score            | 4.41 (2.00)   |
| ASDAS score             | 2.51 (0.68)   |
| C-reactive protein (mg/dL) | 1.59 (2.78)   |
| Erythrocyte sedimentation rate (mm/h) | 20.16 (21.90) |
| Treatment for spondyloarthritis, n (%) | 10 (45.45) |
| Anti-tumor necrosis factor therapy |               |
| Methotrexate            | 4 (18.18)     |
| Non-hormonal anti-inflammatory agents | 4 (18.18) |
| No treatment            | 4 (18.18)     |
| ASDAS, ankylosing spondylitis activity score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SD, standard deviation. |

| Table 2. Metabolic and cardiovascular parameters (n=22). |
|-------------------------|-----------------|
| **Parameter**           | **Value, mean (SD)** |
| Abdominal waist measurement (cm) | 84.28 (12.12) |
| Body mass index (kg/m²) | 24.82 (4.70) |
| Systolic/diastolic blood pressure (mmHg) | 119.77 (14.26) / 77.72 (9.84) |
| Homocysteine (µmol/L) | 10.44 (4.15) |
| Lipids (mg/dL) |               |
| Total cholesterol     | 178.60 (28.18) |
| High density lipoprotein cholesterol | 51.10 (16.18) |
| Low density lipoprotein cholesterol | 108.60 (22.25) |
| Triglycerides         | 92.85 (43.64)  |
| Fasting glucose (mg/dL) | 94.47 (16.33)  |
| Uric acid (mg/dL)     | 5.08 (1.48)    |
| Framingham score      | 4.97 (6.25)    |
| SD, standard deviation. |               |
area and various metabolic parameters (abdominal waist measurement, BMI, total cholesterol, and triglycerides). In addition, as expected, there was a statistically significant correlation between QIMT and age ($r=0.580; p=0.005$); there was no statistically significant correlation between QIMT and disease duration or triglycerides.

### Table 3. Carotid artery, sacroilium, and Achilles tendon ultrasound parameters (n=22).

| Parameter                        | Value, mean (SD) |
|----------------------------------|------------------|
| **Carotid artery**               |                  |
| RF-QIMT (mm)                     | 0.643 (0.16)     |
| Expected QIMTa (mm)              | 0.529 (0.10)     |
| Carotid diameter (mm)            | 6.98 (0.82)      |
| cRI (R)                          | 0.67 (0.12)      |
| cRI (L)                          | 0.82 (0.38)      |
| **Sacroilium**                   |                  |
| sRI (R)                          | 1.10 (0.97)      |
| sRI (L)                          | 0.94 (0.13)      |
| AsGs (R) (cm²)                   | 1.01 (0.60)      |
| AsGs (L)                         | 1.14 (0.48)      |
| **Achilles tendon**              |                  |
| TGS (R) (cm)                     | 0.42 (0.11)      |
| TGS (L)                          | 0.46 (0.12)      |

*aExpected QIMT according to age-categorized values (based on the standard deviation for a sample population aged ≥25 years): mean values of 0.4–0.65 mm is normal.*

AsGs, sacral area measurement; cRI, carotid RI; L, left; QIMT, quality intima-media thickness; R, right; RF, radiofrequency; RI, resistive index; SD, standard deviation; sRI, sacroiliac RI; TGS, Achilles tendon measurement.

### Table 4. Significant correlations found between parameters using Spearman’s and Pearson’s Correlation analysis.

| Parameters                        | r (p-value) | 
|-----------------------------------|-------------|
| BASDAI and ASDAS                  | 0.635 (p=0.01) |
| BASFI and homocysteine            | 0.738 (p=0.037) |
| BASFI and BMI                     | 0.556 (p<0.01) |
| RF-QIMT and sRI (L)               | 0.482 (p=0.037) |
| RF-QIMT and Framingham score      | 0.537 (p=0.012) |
| Expected QIMT and Framingham score| 0.915 (p<0.01) |
| sRI (R) and ESR                   | 0.506 (p=0.027) |
| sRI (R) and cRI (R)               | 0.816 (p<0.01) |
| cRI (R) and cRI (L)               | 0.847 (p<0.01) |
| AsGs (L) and AsGs (R)             | 0.733 (p<0.01) |
| AsGs (L) and abdominal waist measurement| 0.381 (p=0.044) |
| AsGs (L) and BMI                  | 0.459 (p=0.032) |
| TGS (L) and TGS (R)               | 0.518 (p=0.016) |

ASDAS, ankylosing spondylitis activity score; AsGs, sacral area measurement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; cRI, carotid RI; ESR, erythrocyte sedimentation rate; L, left; QIMT, quality intima-media thickness; R, right; RF, radiofrequency; RI, resistive index (decrease); sRI, sacroiliac RI; TGS, Achilles tendon measurement.

### Discussion

Spectral Doppler ultrasound can demonstrate the active phase of the inflammatory process in sacroiliitis. A reduced RI value indicates a reduction in the resistance to blood flow within vessels, reflecting inflammation. The RI is high outside of the period of active inflammation and in healthy people. Spectral Doppler ultrasound can also help in evaluating the response to therapy; along with an improvement in clinical symptoms, an increase in RI indicates a successful response. To the best of our knowledge, the current study is the first to present new ultrasonographic variables including an evaluation of automated measurement of the medial and intimal layer by radiofrequency and the correlation with other variables such as sacroiliac and carotid resistance. Unfortunately, in the current study, sacroiliac joint inflammation was not marked, because only 14 sacroiliac joints had a low RI, with a mean value of 0.71 (below the value of 0.97 reported for healthy volunteers in the literature). Nonetheless, a significant correlation was found between sacroiliac RI and ESR. In the future, we hope to extend our investigations to a larger sample of patients with higher activity or in patients with/without sacroiliac bone edema.
Patients with chronic inflammatory rheumatologic diseases such as spondyloarthritis are exposed to systemic inflammatory reactions as well as articular inflammation. Consequently, this exposes them to the effects of chronic inflammation, including macrovascular and microvascular changes.\textsuperscript{30–33} Chronic inflammation is a key factor involved in the early stages of the development of cardiovascular diseases, and its detection could help with prevention. Ultrasonography is not only capable of detecting inflammatory reactions in joints but also of detecting alterations in large blood vessels, such as the carotid artery, caused by chronic systemic inflammation. While an evaluation by gray scale cannot detect the real articular space because it is too narrow and, therefore, difficult to obtain an acoustic window, it is important to assess the vascular flow of the iliac and sacral arteria at the sacroiliac articular space, characterizing a hemodynamic response toward the presence of an inflammatory process.

Carotid ultrasonography measuring IMT is a noninvasive method of detecting subclinical atherosclerosis. Increased IMT values reflect local abnormalities that correlate with widespread histologically proven atherosclerosis.\textsuperscript{34–37} Measurement of IMT has predictive value in terms of cardiovascular events, independent of traditional risk factors.\textsuperscript{38–42} Common carotid artery IMT shows positive correlations with the duration of inflammatory articular disease, laboratory parameters reflecting inflammation, age, and traditional risk factors for cardiovascular disease.\textsuperscript{43–46} Cardiology societies suggest that evaluation of common carotid artery IMT should form part of the medical assessment of patients at increased cardiovascular risk,\textsuperscript{49} and rheumatology guidelines recommend that patients with inflammatory arthritis should undergo ultrasound evaluation of the carotid arteries.\textsuperscript{47,48,51} Evaluation of these criteria in arthritis was established based on histologic evidence.\textsuperscript{38–35}

In the current study, though the study population had, on average, a normal lipid profile, subclinical alterations consistent with atherosclerosis were seen based on an increased mean RF-QIMT. A previous study in patients with chronic inflammatory articular disease, specifically psoriatic arthritis, demonstrated the relationship between such disorders and an increased risk of subclinical atherosclerosis and cardiovascular events using the QIMT method.\textsuperscript{56}

The use of ultrasonography in the field of rheumatology is increasingly common because it is noninvasive, low cost, and widely accessible. Techniques are evolving. Ultrasound with spectral Doppler using the QIMT technique is an appropriate imaging method for inflammatory reactions; it enables visualization of atherosclerotic changes in the vessel wall caused by the chronic inflammatory activity that occurs in rheumatologic diseases such as spondyloarthritis.

Limitations of the current study include the heterogeneity of the patients’ results and the small number of participants. The latter is largely due to the fact that this patient group included individuals with mobility problems and other disabilities due to chronic disease, which make participation difficult for patients. All ultrasound measurements, including the carotid artery assessments, were performed by a rheumatologist. However, the rheumatologist had extensive experience in ultrasonography, and it has been shown that rheumatologists who are not expert in vascular ultrasound can perform reliable carotid RF-QIMT assessments.\textsuperscript{57} Furthermore, while differences in RI values between right and left could possibly reflect poor reproducibility, it must be borne in mind that bilateral sacroiliac inflammation does not always exist; thus, right/left differences are likely to reflect the latter observation. Finally, while the findings from our study provide supportive evidence, it is important to note that cross-sectional analysis does not provide information on causality.

In conclusion, our study provides evidence supporting the use of ultrasound for the detection of inflammatory activity in joints and in blood vessels, and provides evidence of the lesions caused by widespread inflammation in these patients. The study also shows that there were positive correlations between these ultrasound findings and parameters reflecting patients’ metabolic profile and alterations in inflammatory markers.

\textbf{Contributions:} All the medical team of the Pontifical Catholic University of Campinas contributed with the methodological and clinical aspects. Guilherme B Damian was accountable for medical writing and is a full-time employee of UCB, Sao Paulo, Brazil.

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