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- ABSTRACT -

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DOCTORAL THESIS - ABSTRACT

THE CONTRIBUTION OF ANKLE ULTRASOUND EVALUATION TO RHEUMATOID ARTHRITIS ACTIVITY

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1. **Introduction**

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which, in the absence of treatment or in the case of late administration, can cause significant joint damage, subsequently with functional impotence and affect the quality of life. RA mainly affects small joints, but also large ones, usually symmetrical. Among the large joints affected by RA, the ankle is frequently reported in patients' symptoms from the beginning. However, clinicians acknowledge that they pay little attention to the ankle and hindfoot, compared to other joints, such as the hand, and even to other large joints, such as the elbows, although the frequency of their clinical involvement is reported to be smaller than that of the ankles.

The clinical examination is the first and the most important step in the evaluation of the patient with RA, from the moment of diagnosis and later in the evaluation of the disease. Examining the ankles could be more difficult, on the one hand because of the anatomical complexity of this joint (composed from very close and overlapping anatomical structures), and on the other hand, because of the possible presence of local factors that can lead to misinterpretation of ankle changes as related to RA (obesity, venous insufficiency, edema of various causes). This is the reason why the information provided by joint ultrasound, complementary to the clinical examination in assessing joint inflammation, is very necessary for the ankle, which is able not only to bring new information, but also to confirm or reject the results of the clinical examination. Its role in the diagnosis of RA is already proven, the recommendation of the European League against Rheumatism (EULAR) for the use of ultrasound being mentioned in the 2010 American College of Rheumatology (ACR) and EULAR classification criteria of RA, in order to increase diagnostic certainty.

Disease activity is most frequently assessed by composite indices, the most widely used in both research and current practice being DAS28 („disease activity score") and SDAI („Simple Disease Activity Index"), none of them taking into account the ankle and foot, considering it has been shown that the inclusion of these joints does not significantly influence the assessment of disease activity [1]. However, in a recently published study, it was shown that patients considered to be in remission may present with ultrasound synovitis in the small joints of the foot, with a predictive role for the reactivation of the disease (loss of remission), emphasizing that omission of the foot joints in the evaluation of the activity of the disease leads to its underestimation [2]. Ultrasound thus proves its usefulness in assessing the activity of the disease, capturing persistent inflammation, confirming clinical findings, but also detecting subclinical inflammation, omitted by the clinical examination. The persistence of inflammatory ultrasound changes, especially those with power Doppler (PD) activity, poses a risk for radiological progression of structural lesions, subsequently with functional disability, accentuated at the ankle and foot (influencing gait) and affecting the quality of life. Ultrasound and clinically expressed inflammation may improve after initiation of biological therapy, but this treatment becomes more valuable if initiated before the onset of irreversible structural changes [3].

Thus, we believe that joint inflammation should be identified early, both clinically and with ultrasound, the latter providing very useful information about the ankle, to compensate for the low sensitivity, but especially for the low specificity of clinical examination at this level.

However, the ankle has not received much attention so far, but interest is growing in recent years, therefore ultrasound evaluation needs a more elaborate, standardized protocol, with more information about the subtalar joint (STJ). Also, due to the low attention given in

research studies, the inter-observer variability of ankle ultrasound is high compared to that at the small joints of the hands and feet.

In order to correctly interpret the ultrasound information as pathological, it would be useful initially to evaluate the ultrasound in normal subjects, in order to identify possible physiological changes, later the pathological ones. Discrimination between physiological and pathological elements remains a challenge, especially since ultrasound does not use measurements, which are relative to each individual, and there is also no threshold to make a difference.

To date, magnetic resonance imaging (MRI) continues to be the gold standard in musculoskeletal imaging. However, in recent years, ultrasound has shown significant sensitivity and specificity in the detection of inflammatory lesions, but most studies have been performed on the hands [4]. Regarding the ankle, there is little comparative data between ultrasound and MRI and therefore, before using ultrasound evaluation in a study, the method must be validated by comparison with MRI, for the accuracy of the data.

It is not yet possible to say with certainty how frequent are the inflammatory lesions of the ankle, expressed clinically and on ultrasound, the data in the literature being few and discordant. Additional studies are needed for a complete analysis on a homogeneous study population.

Is ultrasound-detected inflammation of the ankle in a patient with RA important? Does it reflect the activity of the disease or does it develop in parallel with it? Composite scores are sufficient to assess disease activity or there is joint inflammation that is not captured by them, despite reaching the therapeutic goal (remission or low disease activity - LDA), which may progress, radiographically without being therapeutically sanctioned or by adopting a tapering scheme. We notice that there are many unanswered questions regarding the contribution of the ankle to RA activity and evolution.

In these conditions, the doctoral thesis aims to elucidate the answer to the questions regarding the relevance of detecting clinical and ultrasound inflammation in the ankle of patients with RA.

2. **Objectives**

The study has the following objectives:

- description of ultrasound changes in the ankle in healthy subjects;
- comparison of the ultrasound method with MRI (reference imaging method) in detecting inflammatory lesions in the ankle;
- evaluation of the frequency of ultrasound inflammatory lesions in the ankle of RA patients;
- identification of correlations between the existence of ankle ultrasound-detected inflammatory lesions and RA activity;
- evaluation of the ability to predict disease activity by ultrasound inflammatory lesions;
- clinical and ultrasound evaluation of the ankle in patients with RA in remission.

3. **Materials and methods**

3.1. Selection of patients

In this prospective study, patients were recruited from the Outpatient Clinic of the Clinical Center for Rheumatic Diseases „Dr. Ion Stoia" Bucharest, between January and December 2018. The selection was random, in the order of presentation. Patients over 18 years of age and a definite diagnosis of RA were included in the study, according to the ACR-EULAR 2010 classification criteria of RA [5]. During the same period, a control group of

healthy subjects was selected, without a history of inflammatory or degenerative joint disease, without current joint symptoms. The exclusion criteria from the study were: the presence of any ankle deformity (either in the context of RA or any other cause), personal history of trauma or surgery in the ankle and foot, comorbidities that influence the assessment of joint count (fibromyalgia, depression, complex regional pain syndrome), pregnancy, parenteral glucocorticoid therapy (pulse therapy, intramuscular injections, intra-articular and peri-articular injections) in the month prior to study inclusion. Drugs that may influence ultrasound evaluation were allowed as follows: oral glucocorticoid treatment at a maximum dose of 10 mg/day prednisone equivalent if the dose was stable (unchanged in the month prior to study); nonsteroidal anti-inflammatory drugs (NSAIDs) at stable doses (including the last week before inclusion in the study). For the group of patients who underwent ankle MRI, in addition to the mentioned exclusion criteria, the contraindications imposed by MRI (pacemaker, prosthesis or other metal, ferromagnetic implants, which do not allow this investigation) were applied. Both patients and healthy subjects agreed to participate in the study by signing an informed consent. The study was approved by the local ethics commission of the Clinical Center for Rheumatic Diseases „Dr. Ion Stoia" Bucharest. Individually, for each study participant, questionnaires, clinical evaluation, laboratory tests and ultrasound evaluation of the ankle were performed on the same day. In addition, in a subset of patients with RA, as well as in healthy subjects, MRI of the ankle was performed on the same day or within a maximum of 72 hours after the rest of the assessments, depending on accessibility.

3.2. Clinical evaluation

All patients and healthy subjects were clinically examined by the same senior rheumatologist, blind to other investigation results, in order not to be influenced.

From the anamnesis and from the medical documents of the patients, the following data were registered: age, sex, duration of the disease (calculated from the beginning of the first symptoms until enrollment in the study), current antirheumatic treatment and comorbidities that may influence the clinical evaluation of the ankle, such as diabetes, obesity, chronic venous insufficiency of the lower limbs.

The examination of the patients consisted in joint evaluation (counting both the sets of 28 and 44 joints) registering the presence of pain and/or swelling at the level of each of them. Special attention was paid to the ankles. At this level, inspection, palpation and active mobilization were performed (trying to facilitate the exposure of the ankle and hindfoot joints to the clinical examination), separately for each compartment, noting the presence of pain and/or swelling. Patients with pain and/or swelling at this level were labeled as patients with symptomatic ankles, while those with no symptoms were labeled patients with asymptomatic ankles. In addition, in the clinical examination of this region, the presence of non-rheumatic pathological changes was also recorded: excess fat deposition (in the context of obesity), leg edema, changes that hinder clinical examination of the ankles, decreasing its accuracy. Following joint evaluation, tender joint counts (TJC53 and TJC28) and swollen joint counts (TJC44 and NAT28) were recorded. Both the patient (PtGA) and the physician (PhGA) global assessment of the disease were reported by completing a visual analog scale of 0-10 cm. In addition, to assess the quality of life, patients independently completed the HAQ questionnaire.

3.3. Laboratory workup

The following laboratory tests were determined in all patients: acute phase reactants (C-reactive protein - CRP; erythrocyte sedimentation rate - ESR) and autoimmunity serology (rheumatoid factors - RF and anti-citrullinated protein antibodies - ACPA respectively). With the help of clinical parameters (TJC28 and SJC28), PtGA and acute phase reactants, it was possible to calculate the composite indices for the evaluation of the disease activity: DAS28 using ESR [6], DAS28 using CRP [7], DAS44 (given that the subject of the present study is the contribution of the ankle to the activity of the disease, and the rest of the composite indices

omit the ankle from the joint evaluation) [8-10], as well as SDAI [11]. To define remission, we used in addition to the mentioned composite indices, the Boolean definition [12]. All recorded clinical and laboratory data were noted in the evaluation form of each patient in the study.

3.4. Ultrasound evaluation

All ultrasound examinations were performed by the same senior rheumatologist, with over 8 years of experience in musculoskeletal ultrasound, without knowledge of the clinical and laboratory results All patients underwent ultrasound of both ankles. Healthy subjects performed ultrasound on the right ankle (dominant ankle), the same anatomical region being subsequently evaluated on MRI.

During the entire study, the same ultrasound scanner was used, Esaote MyLabTwice, equipped with a linear probe with a frequency of 12-18 MHz. The ultrasound evaluation consisted initially in the examination of the ankles in mode B (gray scale - GS), later the evaluation of PD to visualize the vascularization at the level of the identified intra-articular and peri-articular lesions. The device settings were optimized before the start of the study, remaining constant for all evaluations.

The following anatomical structures were evaluated: tibiotalar joint (TTJ; anterior and posterior recess), STJ (or talocalcaneal joint; mid-anterior, latero-posterior and posterior section), talonavicular joint (TNJ), tibialis anterior tendon (TAT), extensor hallucis longus tendon (EHLT), extensor digitorum longus tendon (EDLT), tibialis posterior tendon (TPT), flexor digitorum longus tendon (FDLT), flexor hallucis longus tendon (FHLT), peroneus longus tendon (PLT), peroneus brevis tendon (PBT). Also, at the calcaneus level, the Achilles tendon (AT) and the plantar fascia (PF) were evaluated. To increase the sensitivity of the imaging method, the evaluation was done both statically and dynamically. The following inflammatory lesions were recorded: joint synovial hypertrophy (SH), intra-articular fluid collection (FC), tenosynovitis, retro-calcaneal bursitis, calcaneal enthesopathy, plantar fasciitis and sub-calcaneal panniculitis.

The interpretation of the recorded changes complied with the OMERACT definitions for ultrasound-detected pathological lesions [13]. These changes were recorded as present or absent, subsequently, joint SH (excluding FC) was graded on a semi-quantitative scale from 0-3 in both GS and PD [14-16]. For the joints evaluated in several sections (several recesses), the highest score recorded at the level of a recess was assigned to that joint. Intra-articular FC was recorded in a binary system (present or absent). Its meaning as an expression of joint inflammation being uncertain, its scoring [14] was performed only for the accuracy of the concordance of the two imaging methods, both in healthy subjects and RA patients.

Regarding tenosynovitis, in order to increase the accuracy of the comparison of the ultrasound evaluation with MRI results, the presence of tenosynovitis was recorded along with its components (FC and SH inside the tendon sheath). Scoring of tenosynovitis (regardless of the content of the synovial sheath) was done on a semi-quantitative scale, from 0-3, both in GS and in PD [17].

3.5. MRI evaluation

MRI of the ankle and hindfoot, respectively, was performed in all healthy subjects (native MRI, for ethical reasons) and in a subgroup of patients with RA (contrast-enhanced MRI), in order of accessibility to this investigation, so that the evaluation was made on the same day as the other investigations or within a maximum of 3 days. The evaluation was performed unilaterally, at one ankle, its choice for MRI examination being made as follows: the symptomatic ankle in patients with unilateral ankle involvement, respectively right ankle (this being dominant in most individuals) in patients with bilateral ankle involvement, patients with asymptomatic ankles and healthy subjects. All MRI evaluations were performed by the same senior imaging physician, without knowledge of the results of clinical and laboratory investigations. The examinations were performed on a General Electric Optimal 450 WGEM

device, 1.5 Tesla, using a dedicated ankle antenna, HD, with 8 transmission channels. The images obtained were analyzed and interpreted according to the model recommended by OMERACT-RAMRIS, adapted for the examination of the ankle and hindfoot [18-20]. The same anatomical structures were evaluated as on ultrasound: TTJ, STJ, TNJ, TAT, EHLT, EDLT, TPT, FDLT, FHLT, PLT, PBT, as well as AT and FP. The pathological lesions followed were: intra-articular SH and FC, tenosynovitis and bursitis. In the absence of contrast, the evaluation of native MRI cannot make a definite difference between synovitis (SH) and FC, highlighting only the distension of the capsule or synovial sheath. The synovial, being vascularized, shows the intensification of the MRI signal after the administration of the contrast substance. Synovitis (SH) and tenosynovitis were interpreted, subsequently quantified on a scale of 0-3, according to OMERACT recommendations [21, 22]. FC was recorded dichotomously (absent or present). Analogous to synovitis scoring on a 0-3 scale, intra-articular FC scoring was performed only in studies that compared the two imaging methods (in healthy subjects as well as in RA patients), in order to increase the accuracy of the agreement.

3.6. Statistical analysis

The normality of the distribution was assessed using descriptive numerical and visual statistics, as well as Kolmogorov-Smirnov tests. Continuous variables were expressed as "mean ± standard deviation (SD)" if distributed normally, or as "median (interquartile range - IQR)" if distributed abnormally. The dichotomous variables were expressed as "absolute frequency (percentage of group)" or strictly percentage of group. The differences of the continuous variables between the subgroups of the dichotomous variables or between the subgroups of the variables with more than two levels were studied with Mann Whitney U tests, respectively with Kruskal-Wallis tests. To identify significant differences between the categories of multi-level nominal variables, post-hoc Bonferoni comparisons of Kruskal-Wallis test results were performed. The association of dichotomous variables was studied with χ^2 tests. To compare MRI and ultrasound in terms of SH grading, the tabulation was reduced to a 2 x 2 table by grouping "absent" with "minimal" and "moderate" with "severe". The performance of ultrasound compared to MRI was evaluated with: overall agreement (OA); positive agreement index (PA); κ (Cohen) index calculated by tabulation (strength of concordance: < 0.2 - poor; 0.21 - 0.40 - acceptable; 0.41 - 0.60 - moderate; 0.61 - 0.80 - good and respectively > 0.80 - very good) [23]; sensitivity; specificity; positive likelihood ratio (PLR; effect of increasing the probability of detection: > 10 - high; 5-10 - moderate and < 5 - low, respectively) [24]; negative likelihood ratio (NLR). The ability of clinical elements to predict ultrasound SH at the ankle was studied using binary logistic regressions and were compared using the McNemar test. The prediction of $DAS28_{CRP}$ was studied with standard linear regression models, built using the automatic linear modeling available in SPSS, with step-by-step selection method, informational criterion for input/elimination and 95% confidence interval. All tests were considered significant if $p < 0.05$ and were performed with IBM SPSS Statistics version 22.0 for Windows (Armonk, NY, IBM Corp.).

4. **Results and discussion**

4.1. General characteristics

This study included 183 patients with RA (table 1), predominantly women (86.3%), with a mean age of 57.3 ± 12.5 years, as well as 25 healthy subjects, predominantly women. (84%), with a mean age of 54.6 ± 11.8 years.

4.2. Assessment of the ankle in healthy subjects - ultrasound compared to MRI

To achieve this goal, 25 healthy subjects were analyzed.

Intra-articular, both ultrasound and MRI showed minimal FC in both TTJ (anterior and posterior recess) and STJ (only in posterior ultrasound recess, mainly in posterior MRI recess;

table 2). Peri-articular, at the level of the tendons, ultrasound, respectively MRI, showed minimal FC in the synovial sheath of the tendons only at the level of the medial compartment (flexor tendons), the most frequently involved being TPT; anterior and lateral compartments (TAT, extensor and peroneal tendons) showing no imaging changes (table 2).

Table 1. General characteristics of RA patients (n = 183)

1. *demographic data*	
women	158 (86,3%)
men	25 (13,7%)
age (years)	57,3 ± 12,5
2. *RA phenotype*	
RA duration (years)	11,2 ± 10,3
RF (UI/mL)	75,3 (0-1600)
FR positive	118 (64,5%)
ACPA (UI/mL)	166,1 (0-530)
ACPA positive	139 (76,0%)
3. *RA activity*	
TJC28	4 (0-25)
TJC44	5 (0-30)
≥ 1 tender ankle	100 (54,6%)
SJC28	1 (0-24)
SJC44	2 (0-28)
≥ 1 swollen ankle	56 (30,6%)
ESR (mm/h)	34 (2-98)
CRP (mg/L)	9,2 (0,2-196)
PtGA (mm)	42,6 ± 25,9
PhGA (mm)	31,5 ± 22,8
$DAS28_{ESR}$	4,4 ± 1,7
$DAS28_{CRP}$	3,8 ± 1,7
$DAS44_{ESR}$	2,9 ± 1,3
SDAI	18,3 ± 15,7
HAQ	1,5 ± 0,8
4. *RA treatment*	
NSAIDs	48 (26,2%)
glucocorticoids	32 (17,5%)
csDMARDs	155 (84,7%)
methotrexate	88 (48,1%)
> 1 csDMARD	17 (9,3%)
bDMARDs	64 (35,0%)
monotherapy bDMARDs	1 (0,5%)
5. *comorbidities*	
diabetes mellitus	17 (9,3%)
hallux valgus	58 (31,7%)
CVI-LL	38 (20,8%)
obesity	4 (2,2%)
pes planus	4 (2,2%)

Notes: continuous variables distributed approximately normally are reported as „mean ± SD"; continuous variables that are not normally distributed are reported as „median (minimum-maximum)"; nominal variables are reported as „absolute frequency (percentage of sample/group)".
Abbreviations: ACPA - anti-citrullinated protein antibodies; b/csDMARD - biologic or conventional synthetic disease-modifying anti-rheumatic drugs; CRP - C-reactive protein; CVI-LL - chronic venous insufficiency of lower limbs; DAS - disease activity score; ESR - erythrocyte sedimentation rate; HAQ - health assessment questionnaire; NSAIDs - non-steroidal anti-inflammatory drugs; Pt/hGA - patient/physician global assessment; RA - rheumatoid arthritis; RF - rheumatoid factor; SDAI - simplified disease activity index; T/SJC - tender/swollen joint count; UI - international units.

The analysis of the results reveals the concordance of the ultrasound results with the MRI findings (table 3), in the detection of changes in healthy subjects, especially in the joints, while in the tendons, although the concordance was lower, the specificity was increased.

Table 2. Ultrasound-MRI comparison of ankle global imaging involvement in healthy subjects (n = 25)

	echo+	*MRI+*	*OA*	*PA*	*κ*	*Se*	*Sp*	*PLR*
TTJ	5	6	88,0%	80,0%	0,65	66,7%	94,7%	12,7
STJ	9	11	92,0%	100%	0,83	81,8%	100%	-
TAT	0	0	-	-	-	-	-	-
EHLT	0	0	-	-	-	-	-	-
EDLT	0	0	-	-	-	-	-	-
PLT	0	0	-	-	-	-	-	-
PBT	0	0	-	-	-	-	-	-
TPT	5	12	72,0%	100%	0,43	41,7%	100%	-
FDLT	4	8	76,0%	75,0%	0,36	37,5%	94,1%	6,4
FHLT	5	8	88,0%	100%	0,69	62,5%	100%	-
AT	0	0	-	-	-	-	-	-
PF	0	0	-	-	-	-	-	-

Notes: the columns "echo+" (present ultrasound involvement) and "MRI+" (present MRI involvement) report the number of patients; the level of statistical significance of the κ indices: $p = 0.001$ (TTJ); $p < 0.001$ (STJ and FHLT); $p = 0.009$ (TPT); $p = 0.044$ (FDLT). Abbreviations: AT - Achilles tendon; EDLT - extensor digitorum longus tendon; EHLT - extensor hallucis longus tendon; FDLT - flexor digitorum longus tendon; FHLT - flexor hallucis longus tendon; MRI - magnetic resonance imaging; OA - overall agreement; PA - positive agreement; PBT - peroneus brevis tendon; PF - plantar fascia; PLR - positive likelihood ratio; PLT - peroneus longus tendon; Se - sensitivity; Sp - specificity; STJ - subtalar joint; TAT - tibialis anterior tendon; TPT - tibialis posterior tendon; TTJ - tibiotalar joint.

An explanation for the low sensitivity of ultrasound in detecting intra-articular FC could be the deep anatomical location of these joints, which makes ultrasound visualization difficult, especially for minimal FC. In addition, when assessing the posterior recess of the TTJ, the patient's different position on MRI compared to ultrasound (ventral decubitus that favors FC migration in the anterior recess) may explain the more frequent detection of this change by MRI. Regarding the ultrasound examination of the tendons in the medial compartment, the minimal fluid accumulation in the synovial sheath of the tendon, immediately infra-malleolar, where they change course, which does not surround the tendon entirely, is considered physiological, being explained by the position of the ultrasound evaluation (patient lying on his back, knee bent at 90°, sole resting on the bed) which determines the sloping migration of the fluid, thus being unreported on ultrasound.

In this study, it was demonstrated by two imaging methods that healthy subjects do not show synovial proliferation, neither intra-articular nor peri-articular (synovial sheath of tendons), and also do not show pathology with positive Doppler signals, elements that are very important for defining pathological ultrasound results that can be observed in the ankles of patients with RA.

4.3. Evaluation of the ankle in RA patients - ultrasound compared to MRI

For the comparative analysis of the two imaging methods in the ankles of RA patients, the study sample included 50 patients with RA, with a mean age of 55.9 ± 11.2 years, predominantly women (84%).

At the articular level, the ultrasound evaluation of the TTJ had very good agreement with the MRI evaluation, both in terms of detection (including grading) of SH and intra-

articular FC, also recording increased sensitivity and specificity. In contrast, the ultrasound examination of the STJ showed moderately-good agreement with the MRI evaluation, moderately increasing the chance of detecting both SH and FC (table 4).

Table 3. The matrix of cases depending on the presence or absence of imaging impairment (n = 25)

	echo+ and MRI+	*echo+ and MRI -*	*echo- and MRI +*	*echo- and MRI -*
TTJ, anterior recess	3 (12%)	0 (0%)	1 (4%)	21 (84%)
TTJ, posterior recess	2 (8%)	1 (4%)	2 (8%)	20 (80%)
STJ, posterior recess	9 (36%)	0 (0%)	2 (8%)	14 (56%)
STJ, anterior recess	0 (0%)	0 (0%)	2 (8%)	23 (92%)
TAT	0 (0%)	0 (0%)	0 (0%)	25 (100%)
EHLT	0 (0%)	0 (0%)	0 (0%)	25 (100%)
EDLT	0 (0%)	0 (0%)	0 (0%)	25 (100%)
PLT	0 (0%)	0 (0%)	0 (0%)	25 (100%)
PBT	0 (0%)	0 (0%)	0 (0%)	25 (100%)
TPT	5 (20%)	0 (%)	7 (28%)	13 (52%)
FDLT	3 (12%)	1 (4%)	5 (20%)	16 (64%)
FHLT	5 (20%)	0 (0%)	3 (12%)	17 (68%)
AT	0 (0%)	0 (0%)	0 (0%)	25 (100%)
PF	0 (0%)	0 (0%)	0 (0%)	25 (100%)

Notes: the columns "echo+" (present ultrasound involvement) and "MRI+" (present MRI involvement) report the number of patients. Abbreviations:
AT - Achilles tendon; EDLT - extensor digitorum longus tendon; EHLT - extensor hallucis longus tendon; FDLT - flexor digitorum longus tendon; FHLT - flexor hallucis longus tendon; MRI - magnetic resonance imaging; PBT - peroneus brevis tendon; PF - plantar fascia; PLT - peroneus longus tendon; STJ - subtalar joint; TAT - tibialis anterior tendon; TPT - tibialis posterior tendon; TTJ - tibiotalar joint.

At the level of the tendons, the best agreement between the two imaging methods was recorded for tenosynovitis of EDLT. Considering its components separately, the best agreement for SH at the tendon sheath was recorded for PLT, and for FC in the tendon sheath of TAT. Regarding the quantification of tenosynovitis, very good agreement was noted for TPT (table 5).

Analyzing each case, we observed that ultrasound did not detect minimal intra-articular SH and FC, MRI being superior in this situation. The explanation is given by the fact that MRI has the ability to visualize the entire joint, including the deep synovial region, regardless of the overlying structures (excessively represented subcutaneous tissue) [25], while ultrasound can visualize only the superficial region of the joint, which is not involved in the minimal changes of the synovial membrane (synovitis/minimal FC). Also, another reason for the agreement decrease is the fact that, in some situations, ultrasound fails to accurately differentiate SH from FC; old FC becomes hypo-echogenic on ultrasound [26], being easily confused with synovitis.

Theoretically, ultrasound differentiation between synovitis and FC is done by transducer compression of the examined structures, and by Doppler evaluation [13, 27], techniques difficult to perform in the case of the ankle and hindfoot (deep anatomical structures). A particular situation is represented by the STJ, where the recorded agreement was moderate to good, the weakest concordance being recorded for the anterior recess (viewed by

ultrasound from the medial section), probably explained by the lower experience in ultrasound evaluation of this joint (the examination protocol ultrasound of the STJ is not yet standardized).

Table 4. Ultrasound-MRI comparison of ankle articular involvement in RA (n = 50)

	echo+	*MRI+*	*OA*	*PA*	*κ*	*Se*	*Sp*	*PLR*
global involvement (FC and SH)								
TTJ	24	26	92%	95,8%	0,84*	88,5%	95,8%	21,1
TTJant	23	25	92%	95,7%	0,84*	88,0%	96,0%	22,0
TTJpost	16	17	86%	81,2%	0,68*	76,5%	90,9%	8,4
STJ	22	25	78%	81,8%	0,56*	72,0%	84,0%	4,5
STJant	6	21	62%	66,7%	0,14&	19,0%	93,1%	2,8
STJpost	21	24	78%	81,0%	0,56*	70,8%	84,6%	4,6
STJpost+lat	21	24	78%	81,0%	0,56*	70,8%	84,6%	4,6
STJlat	10	24	68%	90,0%	0,35*	37,5%	96,2%	9,8
either	29	33	80%	89,7%	0,58*	78,8%	82,4%	4,5
FC presence								
TTJ	22	25	90%	95,5%	0,80*	84,0%	96,0%	21,0
TTJant	20	23	90%	95,0%	0,80*	82,6%	96,3%	22,3
TTJpost	12	11	90%	75,0%	0,72*	81,8%	92,3%	10,6
STJ	19	21	80%	78,9%	0,58*	71,4%	86,2%	5,2
STJant	4	12	72%	25,0%	0,01&	8,3%	92,1%	1,1
STJpost	16	20	80%	81,3%	0,57*	65,0%	90,0%	6,5
STJpost+lat	18	20	80%	77,8%	0,58*	70,0%	86,7%	5,3
STJlat	6	20	64%	66,7%	0,15&	20,0%	93,3%	3,0
SH presence								
TTJ	14	16	92%	92,9%	0,81*	81,2%	97,1%	28,0
TTJant	13	16	90%	92,3%	0,76*	75,0%	97,1%	25,9
TTJpost	10	13	90%	90,0%	0,72*	69,2%	97,3%	25,6
STJ	15	16	86%	80,0%	0,67*	75,0%	91,2%	8,5
STJant	4	15	74%	75,0%	0,22#	20,0%	97,1%	7,0
STJpost	12	14	88%	83,3%	0,69*	71,4%	94,4%	12,8
STJpost+lat	14	14	88%	78,6%	0.70*	78,6%	91,7%	9,4
STJlat	9	14	86%	88,9%	0,61*	57,1%	97,2%	20,6
grade 2-3 SH								
TTJ	7	5	96%	71,4%	0,81*	100%	95,6%	22,7
TTJant	6	5	98%	83,3%	0,90*	100%	97,8%	45,5
TTJpost	6	2	92%	33,3%	0,47*	100%	91,7%	12,0
STJ	9	2	86%	22,2%	0,32*	100%	85,4%	6,8
STJant	3	1	96%	33,3%	0,49*	100%	95,9%	24,5
STJpost	3	2	94%	33,3%	0,37*	50,0%	95,8%	11,9
STJpost+lat	7	2	90%	28,6%	0,41*	100%	89,6%	9,6
STJlat	7	2	90%	28,6%	0,37*	100%	89,6%	9,6

Notes: the columns "echo+" (present ultrasound involvement) and "MRI+" (present MRI involvement) report the number of patients; significance level of κ indices: * $p \leq 0.007$, # $p < 0.05$; & insignificant; + - positive. Abbreviations: ant - anterior; FC - fluid collection; lat - lateral; MRI - magnetic resonance imaging; OA - overall agreement; PA - positive agreement; PLR - positive likelihood ratio; post - posterior; RA - rheumatoid arthritis; Se - sensitivity; SH - synovial hypertrophy; Sp - specificity; STJ - subtalar joint; TTJ - tibiotalar joint.

Table 5. Ultrasound-MRI comparison of ankle tendon involvement in RA (n = 50)

	echo+	*MRI+*	*OA*	*PA*	*κ*	*Se*	*Sp*	*PLR*
global involvement (FC and SH)								
TAT	3	9	90%	100%	0,45*	33,3%	100%	-&
EHLT	2	5	94%	100%	0,55*	40,0%	100%	-&
EDLT	7	8	94%	85,7%	0,80*	75,0%	97,6%	31,3
PLT	14	14	88%	78,6%	0,70*	78,6%	91,7%	9,5
PBT	11	11	88%	72,7%	0,65*	72,7%	92,3%	9,4
TPT	20	23	78%	80,0%	0,55*	69,6%	85,2%	4,7
FDLT	12	15	76%	83,3%	0,65*	66,7%	94,3%	11,7
FHLT	8	19	78%	100%	0,47*	42,1%	100%	-&
either	29	28	86%	86,2%	0,72*	89,3%	81,8%	4,9
FC presence								
TAT	3	4	98%	100%	0,85*	75,0%	100%	-&
EHLT	1	0	-&	-&	-&	-&	-&	-&
EDLT	6	4	92%	50,0%	0,56*	75,0%	93,5%	11,5
PLT	9	9	80%	44,4%	0,32*	44,4%	87,8%	3,6
PBT	6	3	86%	16,7%	0,16#	33,3%	89,4%	3,1
TPT	14	13	82%	64,3%	0,54*	69,2%	86,5%	5,1
FDLT	8	4	88%	37,5%	0,44*	75,0%	89,1%	6,9
FHLT	7	14	86%	100%	0,59*	50,0%	100%	-&
SH presence								
TAT	3	8	90%	100%	0,50*	37,5%	100%	-&
EHLT	2	5	94%	100%	0,55*	40,0%	100%	-&
EDLT	5	6	94%	80,0%	0,69*	66,7%	97,7%	29,0
PLT	11	11	96%	90,9%	0,88*	90,9%	97,4%	35,0
PBT	9	11	88%	77,8%	0,63*	63,6%	94,9%	12,5
TPT	19	20	82%	78,9%	0,62*	75,0%	86,7%	5,6
FDLT	9	13	84%	77,8%	0,54*	53,8%	94,6%	10,0
FHLT	5	11	88%	100%	0,57*	45,5%	100%	-&
grade 2-3 SH								
TAT	3	5	96%	100%	0,73*	60,0%	100%	-&
EHLT	1	0	-&	-&	-&	-&	-&	-&
EDLT	5	4	94%	60,0%	0,63*	75,0%	95,7%	17,4
PLT	7	10	86%	71,4%	0,51*	50,0%	95,0%	10,0
PBT	3	2	94%	33,3%	0,37*	50,0%	95,8%	11,9
TPT	14	14	96%	92,9%	0,90*	92,9%	97,2%	33,2
FDLT	4	5	90%	50,0%	0,39*	40,0%	95,6%	9,1
FHLT	5	17	76%	100%	0,36*	29,4%	100%	-&

Notes: the columns "echo+" (present ultrasound involvement) and "MRI+" (present MRI involvement) report the number of patients; significance level of κ indices: * $p \leq 0.023$; # insignificant; & incalculable (due to division by 0 or all ultrasound and/or MRI assessments are identical). Abbreviations: EDLT - extensor digitorum longus tendon; EHLT - extensor hallucis longus tendon; FC - fluid collection; FDLT - flexor digitorum longus tendon; FHLT - flexor hallucis longus tendon; MRI - magnetic resonance imaging; OA - overall agreement; PA - positive agreement; PBT - peroneus brevis tendon; PLR - positive likelihood ratio; PLT - peroneus longus tendon; RA - rheumatoid arthritis; Se - sensitivity; SH - synovial hypertrophy; Sp - specificity; TAT - tibialis anterior tendon; TPT - tibialis posterior tendon.

At the level of the tendons, the lowest agreement was registered in the case of TAT, EHLT and FHLT, explained by the low sensitivity of ultrasound in detecting what MRI interprets as minimum SH in the tendon sheath, respectively minimum FC in the tendon sheath. It should be noted that the statistical analysis performed joint by joint, expressed by PA (100% in all 3 tendons), emphasizes that all changes detected by ultrasound in these tendons were confirmed by MRI, the specificity of ultrasound being thus 100%. It was observed that in cases where ultrasound did not detect changes at this level, while MRI showed minimal FC in the tendon sheath, most patients had local changes that made ultrasound examination difficult (obesity, venous insufficiency of the lower limbs), but also ultrasound changes in the form of FC in the posterior recess of the TTJ which can be confused with the FC in the FHLT sheath, with which it can even communicate anatomically. In this situation, the limits of ultrasound for accurate examination of deep structures must be recognized, especially in the case of a richly represented subcutaneous tissue.

4.4. Ultrasound evaluation of the frequency of inflammatory lesions of the ankle in RA

Of the entire study group (n = 183 patients), 83.6% had inflammatory ultrasound changes in the ankle and hindfoot. The changes were registered bilaterally in 41.5% of patients, and unilaterally in 78.7% of patients. Also, 55.2% presented on ultrasound at least one joint with intra-articular damage (FC and/or SH), while synovitis (intra-articular SH) was present in 53.0% of patients. Peri-articular changes were detected in 55.7% of patients, tenosynovitis being recorded in 52.5% of patients.

The most frequent ultrasound lesion found in the studied group was FC at the level of the STJ, present in 49.2% of patients, followed by SH of the TTJ and tenosynovitis of TPT, both present in 40.4% of patients. Synovitis occurs most frequently in the TTJ (40.4%), followed by STJ (31.1%) and TNJ (28.4%; table 6, 7), respectively.

Regarding TTJ, it was observed that most of the information was obtained from the evaluation of the anterior recess. In contrast, for STJ, most information appears to be obtained from scanning the posterior recess in the posterior section, compared to the assessment of the posterior recess in the lateral section, respectively the anterior recess in the medial section (table 6).

At the level of the ankle and hindfoot, ultrasound detected tenosynovitis, retro-calcaneal bursitis, calcaneal enthesitis and sub-calcaneal panniculitis. In RA, tenosynovitis was most common in TPT (40.4%), followed by PLT (23.0%) and PBT (18.0%). The PD technique showed vascularization in the intra-articular synovitis, in 17.5% of patients; the activity of tenosynovitis, assessed by the presence of the PD signal, was present in 42.6% of patients, the most common, as well as changes in GS, being noticed at the level of TPT (33.3%).

As expected, the subgroup of symptomatic patients in the ankle and hindfoot presented several inflammatory ultrasound lesions, both in GS (92.5% of symptomatic patients compared to 71.1% of asymptomatic patients; $p < 0.001$), as well as in PD mode (68.2% of symptomatic patients compared to 22.4% of asymptomatic patients; $p < 0.001$). It is important to mention the ability of ultrasound to detect inflammatory lesions (table 8, 9), sometimes active (PD signal present), even in the absence of symptoms in the ankle (expression of subclinical inflammation).

We noticed the low incidence of the PD signal at the ankle joints. This observation can be explained by the low sensitivity of PD for large joints, as well as for deep anatomical areas, both situations being found in the case of TTJ and STJ. In addition, at the level of TTJ, in the anterior section, where the anterior articular recess is evaluated, the dorsalis pedis artery is interposed in the examination of the vascularization of the synovial TTJ, making it difficult to examine by creating artifacts. The same low incidence of PD vascular signal at the TTJ level was observed by other authors [28, 29]. In this regard, to increase the sensitivity of PD, Suzuki and colleagues [30] recommend the inclusion of lateral and medial section assessment of the

anterior recess in the TTJ ultrasound evaluation protocol. We observe the same pattern for STJ, the PD signal being detected only in the medial and lateral sections of the joint.

Table 6. The frequency of articular ultrasound inflammatory modifications in RA patients (n = 183)

	TTJ	**STJ**	**TNJ**
number of patients with:			
≥ 1 ankle with overall involvement	93 (50,8%)	106 (57,9%)	64 (35,0%)
bilateral overall involvement	42 (23,0%)	43 (23,5%)	19 (10,4%)
≥ 1 ankle with FC	69 (37,7%)	90 (49,2%)	29 (15,8%)
bilateral FC	25 (13,7%)	31 (16,9%)	6 (3,3%)
≥ 1 ankle with SH	74 (40,4%)	57 (31,1%)	52 (28,4%)
bilateral SH	35 (19,1%)	16 (8,7%)	15 (8,2%)
≥ 1 ankle with grade 0	148 (80,9%)	164 (89,6%)	167 (91,3%)
bilateral grade 0	109 (59,6%)	125 (68,3%)	131 (71,6%)
≥ 1 ankle with grade 1	42 (23,0%)	30 (16,4%)	37 (18,6%)
bilateral grade 1	17 (9,3%)	22 (12,0%)	13 (7,1%)
≥ 1 ankle with grade 2	38 (20,8%)	31 (19,9%)	16 (8,7%)
bilateral grade 2	11 (6,0%)	4 (2,2%)	1 (0,6%)
≥ 1 ankle with grade 3	12 (6,6%)	7 (3,8%)	8 (4,4%)
bilateral grad 3	1 (0,6%)	0	2 (1,1%)
≥ 1 ankle with PD	14 (7,7%)	14 (7,7%)	32 (17,5%)
bilateral PD	6 (3,3%)	6 (3,3%)	14 (7,7%)

Abbreviations: FC - fluid collection; PD - power Doppler; RA - rheumatoid arthritis; SH - synovial hypertrophy; STJ - subtalar joint; TNJ - talonavicular joint TTJ - tibiotalar joint.

Table 7. The frequency of peri-articular ultrasound inflammatory modifications in RA patients (n = 183)

	≥ 1 ankle involved	*bilateral involvement*	*≥ 1 ankle with grade 2-3*	*bilateral grade 2-3*	*≥ 1 ankle with Doppler*	*bilateral Doppler signal*
TAT	14 (7,7%)	3 (1,6%)	11 (6,0%)	3 (1,6%)	13 (7,1%)	6 (3,3%)
EHLT	7 (3,8%)	4 (2,2%)	6 (3,3%)	1 (0,6%)	7 (3,8%)	4 (2,2%)
EDLT	27 (14,8%)	5 (2,7%)	16 (8,5%)	3 (1,6%)	20 (10,9%)	16 (8,7%)
PLT	42 (23,0%)	10 (5,5%)	28 (15,3%)	8 (4,4%)	33 (18,0%)	17 (9,3%)
PBT	33 (18,0%)	8 (4,4%)	15 (8,2%)	2 (1,1%)	28 (15,3%)	11 (6,0%)
TPT	74 (40,4%)	29 (15,9%)	48 (26,2%)	21 (11,5%)	61 (33,3%)	43 (23,5%)
FDLT	23 (12,6%)	7 (3,8%)	15 (8,2%)	2 (1,1%)	18 (9,8%)	11 (6,0%)
FHLT	19 (10,4%)	2 (1,1%)	9 (4,9%)	2 (1,1%)	6 (3,3%)	0
AT	13 (7,1%)	2 (1,1%)	-	-	13 (7,1%)	6 (3,3%)
PF	13 (7,1%)	2 (1,1%)	-	-	0	0
RCB	23 (12.56%)	5 (2,7%)	-	-	9 (4.91%)	3 (1,6%)
SCP	7 (3,8%)	2 (1,1%)	-	-	5 (2,7%)	2 (1,1%)

Abbreviations: AT - Achilles tendon; EDLT - extensor digitorum longus tendon; EHLT - extensor hallucis longus tendon; FDLT - flexor digitorum longus tendon; FHLT - flexor hallucis longus tendon; PBT - peroneus brevis tendon; PF - plantar fascia; PLT - peroneus longus tendon; RA - rheumatoid arthritis; RCB - retro-calcaneal bursitis; SCP - sub-calcaneal panniculitis; TAT - tibialis anterior tendon; TPT - tibialis posterior tendon.

Particular attention was paid to the posterior leg, both to the posterior recess of the TTJ, but especially to the STJ (including the posterior recess), these not being included in the ultrasound evaluation protocol of most research studies. Obviously, from the previous chapters, in which smaller groups of patients were analyzed, in the ultrasound evaluation of the TTJ the

most information was brought by the evaluation of the anterior recess in the anterior section, the statement being true for both SH and FC, most patients with changes in the posterior recess having changes in the anterior recess as well.

Table 8. Comparison of the location and type of ultrasound joint damage in RA patients according to ankle symptoms (n = 183)

		asymptomatic ankles (n = 76)	*≥ 1 symptomatic ankle (n = 107)*	*p*
TTJ	global involvement	28 (36,8%)	65 (60,7%)	0,001
	FC	19 (25,0%)	50 (46,7%)	0,003
	SH	17 (22,4%)	57 (53,3%)	<0,001
	grade 2-3	6 (7,9%)	38 (35,5%)	<0,001
	Doppler signal	3 (3,9%)	11 (10,3%)	0,112
STJ	global involvement	30 (39,5%)	76 (71,0%)	<0,001
	FC	27 (35,5%)	63 (58,9%)	0,002
	SH	9 (11,8%)	48 (44,9%)	<0,001
	grade 2-3	6 (7,9%)	29 (27,1%)	0,001
	Doppler signal	2 (2,6%)	12 (11,2%)	0,031
TNJ	global involvement	16 (21,1%)	48 (44,9%)	0,001
	FC	5 (6,6%)	24 (22,4%)	0,004
	SH	11 (14,5%)	41 (38,3%)	<0,001
	grade 2-3	4 (5,3%)	16 (15,0%)	0,038
	Doppler signal	8 (10,5%)	24 (22,4%)	0,037

Notes: values represent the statistical significance of χ^2 tests (significant if $p < 0.05$); variables are reported as „absolute frequency (percentage of subgroup)".
Abbreviations: FC - fluid collection; RA - rheumatoid arthritis; SH - synovial hypertrophy; STJ - subtalar joint; TNJ - talonavicular joint; TTJ - tibiotalar joint.

Thus, Bruyn and Schmidt's recommendation [31] for ultrasound evaluation of posterior TTJ recess only if the patient has joint symptoms and the ultrasound examination showed no changes, seems plausible in order to save examination time. Regarding the STJ, in the only studies that included its evaluation in their design [32-34], the ultrasound examination was performed only from the medial and lateral section, noting a lower inter-observer variability obtained for the lateral section compared to the medial section, the evaluation of the posterior recess in the posterior section not being included in the study design [33]. Following our results obtained on a representative sample, we verified the observation made following the analysis of smaller groups in previous chapters about the posterior recess of the STJ, namely that it is best viewed in the posterior section, which has the highest sensitivity in detecting synovitis, respectively FC from the posterior recess.

4.5. Clinical and ultrasound damage of the ankle in RA patients in remission

From the sample of 183 RA patients in different degrees of disease activity, we retained for this analysis: 59 (32.2%) patients in remission defined with $DAS28_{CRP}$, 27 (14.8%) patients in SDAI remission and 20 (10.9%) patients in Boolean remission. In these 3 categories of remission (table 10), the general clinical involvement of the ankle showed a similar prevalence (around 30%), with discrepant frequencies of tender and swollen ankles (there were no swollen ankles in patients in Boolean remission, while one-tenth of patients in remission defined with $DAS28_{CRP}$ had at least one swollen ankle).

On average, 77% of patients had ultrasound involvement of the ankles in the 3 remission categories, with similar frequencies of articular SH (33%), articular SH with positive PD signal

(15%), intra-articular FC (60%), tenosynovitis (27%) and tenosynovitis with positive PD signal (15%) (table 10).

Table 9. Comparison of the location and type of peri-articular involvement in RA patients according to ankle symptoms (n = 183)

		asymptomatic ankles (n = 76)	*≥ 1 symptomatic ankle (n = 107)*	*p*
TAT	global involvement	3 (3,9%)	11 (10,3%)	0,112
	grade 2-3	2 (2,6%)	9 (8,4%)	0,105
	Doppler signal	2 (2,6%)	11 (10,3%)	0,047
EHLT	global involvement	0	7 (6,5%)	0,023
	grade 2-3	0	6 (5,6%)	0,036
	Doppler signal	0	7 (6,5%)	0,023
EDLT	global involvement	5 (6,6%)	22 (20,6%)	0,009
	grade 2-3	3 (3,9%)	13 (12,1%)	0,053
	Doppler signal	2 (2,6%)	18 (16,8%)	0,002
PLT	global involvement	9 (11,8%)	33 (30,8%)	0,003
	grade 2-3	6 (7,9%)	22 (20,6%)	0,019
	Doppler signal	5 (6,6%)	28 (26,2%)	0,001
PBT	global involvement	7 (9,2%)	26 (24,3%)	0,009
	grade 2-3	2 (2,6%)	13 (12,1%)	0,021
	Doppler signal	6 (7,9%)	22 (20,6%)	0,019
TPT	global involvement	12 (15,8%)	62 (57,9%)	<0,001
	grade 2-3	6 (7,9%)	42 (39,3%)	<0,001
	Doppler signal	8 (10,5%)	53 (49,5%)	<0,001
FDLT	global involvement	1 (1,3%)	22 (20,6%)	<0,001
	grade 2-3	1 (1,3%)	14 (13,1%)	0,004
	Doppler signal	0	18 (16,8%)	<0,001
FHLT	global involvement	4 (5,3%)	15 (14,0%)	0,056
	grade 2-3	2 (2,6%)	7 (6,5%)	0,228
	Doppler signal	0	6 (5,6%)	0,036
AT	global involvement	3 (3,9%)	10 (9,3%)	0,161
	grade 2-3	3 (3,9%)	10 (9,3%)	0,161
PF	global involvement	3 (3,9%)	10 (9,3%)	0,161

Notes: values represent the statistical significance of $\chi 2$ tests (significant if $p < 0.05$); the variables are reported as "absolute frequency (percentage of subgroup)".

Abbreviations: AT - Achilles tendon; EDLT - extensor digitorum longus tendon; EHLT - extensor hallucis longus tendon; FDLT - flexor digitorum longus tendon; FHLT - flexor hallucis longus tendon; PBT - peroneus brevis tendon; PF - plantar fascia; PLT - peroneus longus tendon; RA - rheumatoid arthritis; TAT - tibialis anterior tendon; TPT - tibialis posterior tendon.

Compared to patients without clinical ankle involvement, those with at least one tender or swollen ankle had significantly higher CRP values (median of 0.34 mg/dL versus 0.19 mg/dL, p = 0.042) and a significantly higher prevalence of inflammatory ultrasound lesions (table 11).

In addition, significantly higher median CRP values were observed when comparing patients with and without intra-articular synovitis (SH), respectively, in GS (table 12); with and without active synovitis (PD present or absent), as well as with and without active tenosynovitis

(PD present or absent), our data emphasizing that CRP is a marker of this residual disease activity.

This study highlights the high frequency of both clinical and especially ultrasound damage of the ankles in patients with RA in remission, regardless of its definition.

Table 10. Prevalence of clinical and ultrasound findings in patients with RA in remission

	remission defined by		
	DAS28$_{CRP}$	SDAI	Boolean
	(n = 59)	*(n = 27)*	*(n = 20)*
TJC ≥ 1	18 (30,5%)	8 (29,6%)	6 (30,0%)
SJC ≥ 1	6 (10,2%)	1 (3,7%)	0 (0%)
clinical ankle involvement[*]	*19 (32,8%)*	*8 (29,6%)*	*6 (30,0%)*
articular ankle SH[#]	21 (35,6%)	8 (29,6%)	7 (35,0%)
articular SH with PD[#]	10 (16,9%)	4 (14,8%)	3 (15,0%)
ankle FC[#]	35 (59,3%)	15 (55,6%)	13 (65,0%)
ankle tenosynovitis[&]	16 (27,1%)	8 (29,6%)	5 (25,0%)
ankle tenosynovitis with PD[&]	9 (15,3%)	4 (14,8%)	3 (15,0%)
positive PD[§]	14 (23,7%)	6 (22,2%)	4 (20,0%)
ultrasound ankle involvement[¶]	*46 (78,0%)*	*20 (74,1%)*	*16 (80,0%)*
deep remission[‡]	*11 (18,6%)*	*7 (25,9%)*	*4 (20,0%)*

Notes: variables are reported as "absolute frequency (percentage of subgroup)"; ultrasound evaluated structures: TTJ, STJ, TAT, EHLT, EDLT, TPT, FDLT, FHLT, PLT, PBT; * defined as at least one tender or swollen ankle; # intra-articular SH, PD signal and FC detected by ultrasound in any of the joints of any ankle; & tenosynovitis and PD signal detected by ultrasound in any tendon of any ankle; § PD signal detected by ultrasound in any of the joints of any ankle or in any tendon of any ankle; ¶ ultrasound defined as SH and/or tenosynovitis in any joint and in any tendon of an ankle; ‡ defined as normal ankles at clinical examination, without SH, tenosynovitis or PD signal at ultrasound evaluation.

Abbreviations: CRP - C-reactive protein; DAS - disease activity score; EDLT - extensor digitorum longus tendon; EHLT - extensor hallucis longus tendon; FC - fluid collection; FDLT - flexor digitorum longus tendon; FHLT - flexor hallucis longus tendon; PBT - peroneus brevis tendon; PD - power Doppler; PLT - peroneus longus tendon; RA - rheumatoid arthritis; SDAI - simplified disease activity index; SH - synovial hypertrophy; SJC - swollen joint count; STJ - subtalar joint; TAT - tibialis anterior tendon; TJC - tender joint count; TNJ - talonavicular joint; TPT - tibialis posterior tendon; TTJ - tibiotalar joint.

4.6. Clinical involvement and intra-articular SH of the ankle - predictive factors for PR activity

Clinical examination of the entire study sample (183 patients) revealed 101 (55.2%) patients with at least one tender ankle and 56 (30.6%) patients with at least one swollen ankle. Regression analysis showed that tender ankles and swollen ankles increased 2.8 times and 3.4 times respectively the risk of ultrasound detection of SH in the ankles. The presence of intra-articular SH in the ankle has been associated with higher disease activity. In addition, a proportional and significant increase in DAS28$_{CRP}$ values was observed with the number of ankle joints presenting SH on ultrasound, as well as with the severity of SH (figure 1).

Table 11. Comparison of ultrasound findings in symptomatic and asymptomatic RA patients in DAS28$_{CRP}$-defined remission (n = 59)

	ankle clinical examination		
	normal (n = 40)	*S/TJC ≥ 1 (n = 19)*	p
intra-articular SH[#]	9 (22.5%)	12 (63.2%)	0,002
intra-articular SH with PD[#]	2 (5.0%)	8 (42.1%)	<0,001
tenosynovitis[&]	7 (17.5%)	9 (47.4%)	0,016
tenosynovitis with PD[&]	2 (5.0%)	7 (36.8%)	0,001
positive PD[§]	4 (10.0%)	10 (52.6%)	<0,001

Note: variables are reported as "absolute frequency (percentage of subgroup)"; ultrasound evaluated structures: TTJ, STJ, TAT, EHLT, EDLT, TPT, FDLT, FHLT, PLT, PBT; # SH, PD signal and ultrasound-detected FC in any joint of an ankle; p values represent the level of statistical significance of the χ^2 tests; & tenosynovitis and PD signal detected by ultrasound in any tendon of any ankle; § PD signal detected by ultrasound in any joint and in any tendon of an ankle. Abbreviations: CRP - C-reactive protein; DAS - disease activity score; EDLT - extensor digitorum longus tendon; EHLT - extensor hallucis longus tendon; FC - fluid collection; FDLT - flexor digitorum longus tendon; FHLT - flexor hallucis longus tendon; PBT - peroneus brevis tendon; PD - power Doppler; PLT - peroneus longus tendon; RA - rheumatoid arthritis; SH - synovial hypertrophy; SJC - swollen joint count; STJ - subtalar joint; TAT - tibialis anterior tendon; TJC - tender joint count; TNJ - talonavicular joint; TPT - tibialis posterior tendon; TTJ - tibiotalar joint..

Table 12. Comparison of RA patients in DAS28$_{CRP}$-defined remission according to the status of global ultrasound involvement

		ultrasound ankle involvement	
	all (n = 59)	*nu (n = 13)*	*da (n = 46)*
women	52 (88,1%)	11 (84,6%)	41 (89,1%)[*]
age (years)	58 (20)	58 (25)	59 (19)[*]
RA duration (years)	9 (15)	10 (16)	9 (14)[*]
NSAIDs	8 (13,6%)	1 (7,7%)	7 (15,6%)[*]
glucocorticoids	9 (15,3%)	1 (7,7%)	8 (17,4%)[*]
csDMARDs	54 (91,5%)	12 (92,3%)	42 (91,3%)[*]
bDMARDs	31 (52,5%)	6 (46.,%)	25 (54,3%)[*]
RF (UI/mL)	46 (139)	117 (75)	35 (153)[*]
RF positive	32 (54,2%)	11 (84,6%)	21 (45,7%)[&]
ACPA (IU/mL)	141 (212)	176 (176)	105 (190)[*]
ACPA positive	39 (66,1%)	11 (84,6%)	28 (60,9%)[*]
TJC28	0 (1)	0 (1)	0 (0)[*]
SJC28	0 (0)	0 (0)	0 (0)[*]
ESR (mm/h)	21 (18)	16 (23)	22 (18)[*]
CRP (mg/dL)	0,26 (0,32)	0,16 (0,20)	0,27 (0,50)[*]
PtGA (mm)	20 (14)	20 (20)	17 (12)[*]
PhGA (mm)	10 (11)	10 (9)	12 (15)[*]
HAQ	0,6 (1,1)	1,4 (1,6)	0,5 (0,9)[*]

Note: differences between subgroups (ultrasound) were assessed with χ^2 tests for nominal variables (e.g. FR positive) and Mann Whitney tests for continuous variables (e.g. FR titer): * insignificant; & p = 0.013. Abbreviations: ACPA - anti-citrullinated protein antibodies; b/csDMARD - biologic or conventional synthetic disease-modifying anti-rheumatic drugs; CRP - C-reactive protein; DAS - disease activity score; ESR - erythrocyte sedimentation rate; HAQ - health assessment questionnaire; NSAIDs - non-steroidal anti-inflammatory drugs; PhGA - physician global assessment; PtGA - patient global assessment; RA - rheumatoid arthritis; RF - rheumatoid factor; STJ - subtalar joint; TJC - tender joint count; IU - international units.

The presence of the PD signal inside ankle joints, at the SH level, produced similar results: the presence of PD signal ($p < 0.001$) and the degree of the PD signal ($p = 0.009$) were associated with higher $DAS28_{CRP}$ values (figure 2). Ankle damage had an independent effect on the activity of the disease defined by $DAS28_{CRP}$: for example, the absence of SH at the ankle decreased independently and significantly $DAS28_{CRP}$ by 0.985 points ($p < 0.001$).

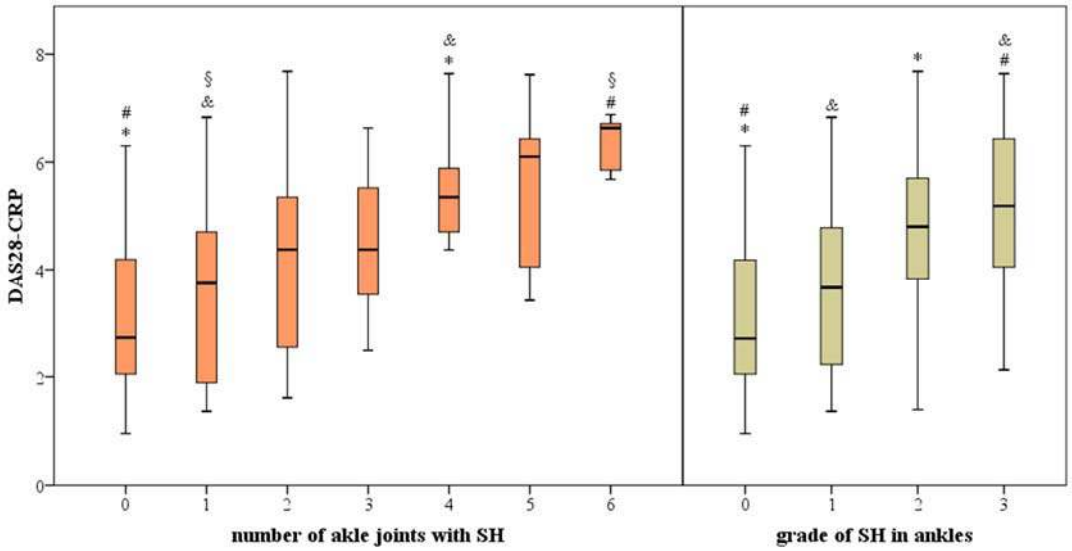


Figure 1. Median $DAS28_{CRP}$ according to the number of ankle joints with SH (left) and the degree of SH in the ankles (right). Notes: Left: the categories contain the number of patients with 0 to 6 ankle joints with SH (left or right TTJ, TNJ and STJ): "0" = 86 patients without SH in the ankle joints; "1" = 28 patients with SH in a single ankle joint (e.g. right TTJ); "2" = 28 patients with SH in 2 ankle joints (e.g. right TNJ and left STJ); "3" = 14 patients (analogue); "4" = 17; "5" = 5; "6" = 5. Kruskal Wallis test (n = 183; 46.5; 6 degrees of freedom; $p < 0.001$) with post-hoc analysis (Bonferoni): * $p < 0.001$; # $p = 0.001$; & $p = 0.003$; § $p = 0.011$. Right: Initially, each TTJ, TNJ and STJ were individually classified. Then, the homologous left and right joints were compared and the highest grade was noted for each joint type (e.g., if a patient had grade 2 SH in the left TTJ and grade 1 SH in the right TTJ, the patient's SH in TTJ was graded 2). Finally, the highest grade of SH of the joint types defined the general grade of ankle SH (e.g., if a patient had grade 2 SH in TTJ, grade 1 SH in TNJ, and no SH in STJ, SH of the patient's ankles was graded 2). There were 85 (46.4%) patients with grade 0, 32 (17.5%) grade 1, 44 (24.1%) grade 2 and 22 (12.0%) grade 3. Kruskal Wallis test (n = 183; 35.2; 3 degrees of freedom; $p < 0.001$) with post-hoc analysis (Bonferoni): *, # $p < 0.001$; & $p = 0.013$. Abbreviations: CRP - C-reactive protein; DAS - disease activity score; SH – synovial hypertrophy; STJ – subtalar joint; TNJ – talonavicular joint; TTJ - tibiotalar joint.

4.7. Ultrasound tenosynovitis of the ankle - significant predictive factor of PR activity

Compared to patients without tenosynovitis of TPT on ultrasound evaluation (59.6%), patients with TPT ultrasound tenosynovitis (40.4%) had a significantly shorter duration of the disease (median 7.0 versus 8.5 years; $p = 0.043$), a higher disease activity (a significantly higher $DAS28_{CRP}$: median 5.0 versus 2.8; $p < 0.001$), a higher impairment of quality of life (a significantly higher HAQ score: median of 1.9 compared to 1.5; $p = 0.037$) and higher titers of RF (median of 123 IU/mL compared to 64 IU/mL; $p = 0.023$), while titers of ACPA were similar ($p > 0.05$). Compared to the presence of ankle pain, the presence of swelling has a

significantly higher capacity (p = 0.034; McNemar test) to predict the presence of ultrasound tenosynovitis.

The presence of tenosynovitis detected by ultrasound in the ankles was associated with higher values of disease activity scores. A further proof of causality was identified: on the one hand, not only the presence, but also the severity (degree), the extension of tenosynovitis at the ankle (number of ankles, respectively number of affected tendons) and its activity (vascularization assessed by PD signals) was associated with increased RA activity (figure 3); on the other hand, the absence of ultrasound detection of tenosynovitis in the ankle was independently and significantly associated with lower disease activity, as assessed by DAS28$_{CRP}$.

In our opinion, the exclusion of ankles from DAS28 was not fully justified, their involvement being closely correlated with PR activity, as our results suggest.

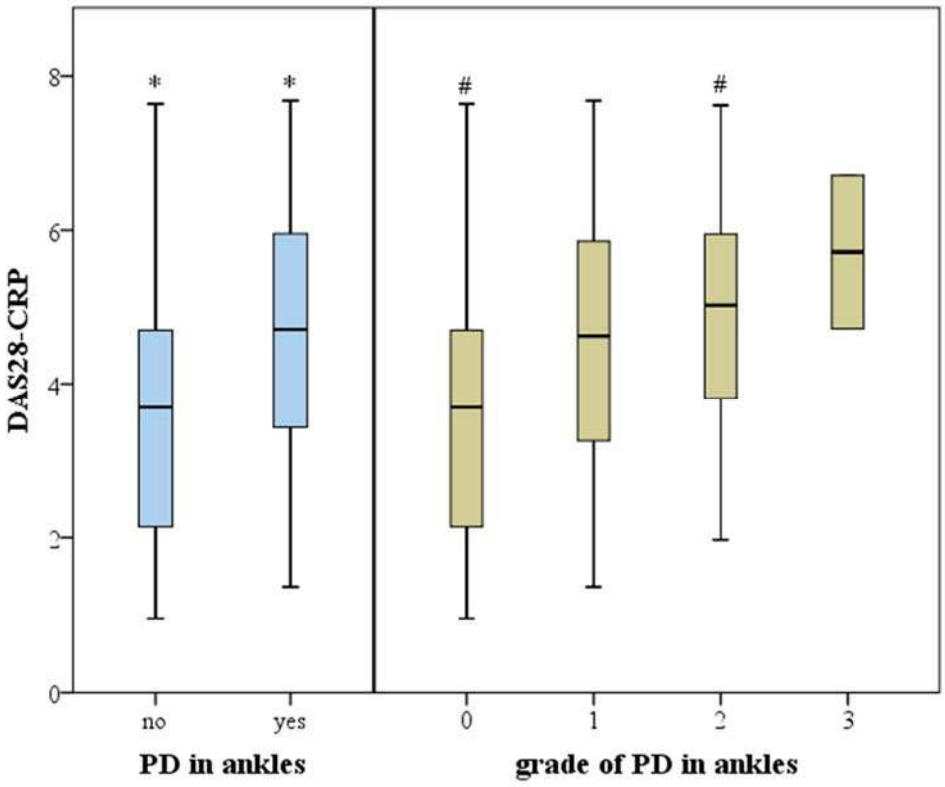
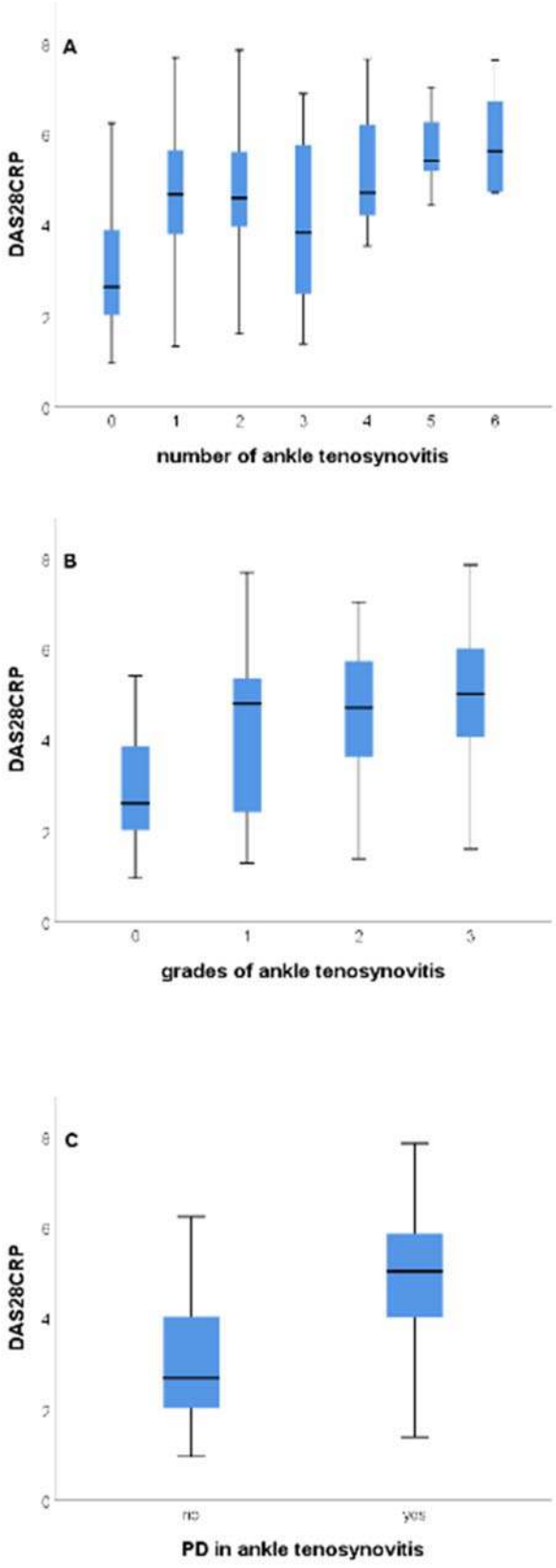


Figure 2. Median DAS28$_{CRP}$ according to the presence of PD signals (left) and the grade of PD signals (right). Notes: For each left and right TTJ, TNJ and STJ the presence and degree of the PD signal were noted. The left and right counterpart joints were then compared and the presence and highest degree of PD signal were noted for each joint type (e.g., if a patient had grade 2 PD signal in the left TTJ and grade 1 PD signal in the right TTJ, the PD signal of the patient's TTJ was graded 2). The presence of PD signals in any joint type defined the presence of PD signals of the ankles, and the highest degree of PD signals among the same joint types defined the general degree of PD signal of the ankle (e.g., if a patient had grade 2 PD signal in TTJ, grade 1 in TNJ and no PD signal in STJ, the degree of PD signal of the patient's ankles was graded 2). There were 45 (24.6%) patients with PD signals in the ankle joints, 138 (75.4%) patients with grade 0, 28 (15.3%) with grade 1, 15 (8.2%) with grade 2 and 2 (1.1%) with grade 3. Left: Mann Whitney test (* $p < 0.001$). Right: Kruskal Wallis test (n = 183; 14.1; 3 degrees of freedom; p = 0.003) with post-hoc analysis (Bonferoni): # p = 0.009. Abbreviations: CRP - C-reactive protein; DAS - disease activity score; SH – synovial hypertrophy; STJ – subtalar joint; TNJ – talonavicular joint; TTJ - tibiotalar joint.



A. The categories contain the number of patients with up to 6 tenosynovitis of the right or left ankle tendons: "0" = 87 patients without ankle tenosynovitis (median $DAS28_{CRP}$ 2.64); "1" = 34 patients with ankle tenosynovitis (e.g. right PBT; median $DAS28_{CRP}$ 4.67); "2" = 24 (4.59); "3" = 18 (3.82); "4" = 7 (4.70); "5" = 7 (5.41); "6" = 6 (5.61). Kruskal Wallis test (n = 183; 52.3; 6 degrees of freedom; $p < 0.001$) with Bonferoni post-hoc analysis showing that "0" differs significantly from "1" ($p = 0.001$), from "2" ($p = 0.001$), "4" ($p = 0.024$), "5" ($p = 0.001$) and "6" ($p = 0.002$).

B. Each tendon of the left and right ankle was graded individually. The left and right homologous tendons were then compared and the highest grade was noted for each type of tendon. The highest degree of all tendon types defined the general degree of tenosynovitis of the patient. Of the total, 47.0% had grade 0 (median $DAS28_{CRP}$ 2.61), 14.2% grade 1 (4.79), 17.5% grade 2 (4.70) and 21.3% grade 3 (5.00). Kruskal Wallis test (n = 183; 50.7; 3 degrees of freedom; $p < 0.001$) with Bonferoni post-hoc analysis showing that "0" differs significantly from "1" ($p = 0.001$), from "2" ($p < 0.001$) and "3" ($p = 0.001$).

C. Overall, 42.6% of patients had no PD signal in all ankle tendons (median $DAS28_{CRP}$ 2.69), and 57.4% of patients had PD signal in at least one ankle tendon (median $DAS28_{CRP}$ 5.02 ; $p < 0.001$; Mann Whitney test).

Figure 3. Median values of $DAS28_{CRP}$ according to the number of ankle tenosynovitis (A), the degree of ankle tenosynovitis (B) and the presence of PD signals in the ankle tendons (C). Abbreviations: CRP - C-reactive protein; DAS - disease activity score; PBT - peroneus brevis tendon; PD – power Doppler.

5. **Limits of the study**

The interpretation of the results of the present study must be made, taking into account some limitations:

- Regarding the comparative assessment of the ankle by the two imaging methods, both in healthy subjects and in RA patients, the study population was represented by a small number of participants, the examinations being performed unilaterally, in the context of difficult MRI accessibility; the data being appropriate for a first report from a larger project. Also, MRI evaluation could not be performed on the same day as ultrasound evaluation in all subjects (which may change the agreement between the two imaging methods).
- In addition, the MRI examination protocol did not include the use of the contrast agent in healthy subjects, which would have increased the accuracy of SH differentiation form intra- and peri-articular FC, for ethical reasons (suspected adverse reactions over time).
- Another limitation of the study is the lack of an inter-observer variability exercise for both ultrasound interpretation and MRI.
- The design of the study did not include conventional radiological examination of the ankle and hindfoot to assess structural damage (possible destruction or joint deformities that may cause, by changing the weight distribution, mechanical secondary damage, both in joint and in tendons).
- Regarding the evaluation of patients with RA in remission, the sample size of the study population was relatively small.
- The design of the study was cross-sectional; therefore, it did not allow the follow-up of patients.
- The clinical examination of the ankle was not performed individually for each anatomical structure of the ankle (tendon, joint); this approach can increase the accuracy of sensitivity and specificity of clinical evaluation in detecting inflammatory lesions which ultrasound identifies in the ankle.

6. **Conclusions**

Musculoskeletal ultrasound at the level of the ankle of RA patients, through the information provided regarding the inflammatory status, allowed in the study to redefine the contribution of the ankle in the RA clinical picture. In summary, the study concluded the following:

- In healthy subjects, ankle ultrasound can detect minimal FC, both intra-articular and around the tendons, the most common being in the posterior recesses and medial compartment, respectively (TPT being the most frequently involved). Therefore, ultrasound detection of minimal intra- and/or peri-articular FC in the ankle should not be clinically relevant in the diagnostic or monitoring assessment of disease activity in RA.
- Ultrasound has proven to be an imaging method with good sensitivity and specificity for the detection of inflammatory lesions in the ankle and hindfoot, generally in good agreement with MRI evaluation.
- Ultrasound evaluation of the ankle of RA patients highlights the increased frequency of inflammatory lesions, of which TTJ synovitis and TPT tenosynovitis are the most common.

- Ultrasound has the ability to highlight inflammation in the ankle and hindfoot, including in the absence of clinical symptoms, changes that may have a potential negative prognosis on structural and functional deterioration. Further studies are needed to monitor the evolution of these lesions.
- RA patients in remission (regardless of the criteria for its definition) may show signs of inflammation in the ankles, both clinically (approximately one-third of patients) and ultrasound (active synovitis and/or tenosynovitis in approximately one-fifth of patients), as well as sustained changes in laboratory parameters of inflammation. In this context, clinical and ultrasound screening of the ankles in RA patients in remission seems an appropriate strategy, taking into account the destructive potential of RA which causes, especially at this level, a severe functional deficit.
- Clinical damage to the ankle, the presence of SH and ultrasound-detected tenosynovitis have a direct relationship with the activity of RA.
- Ankle pain is more sensitive, while ankle swelling is more specific in detecting both SH and tenosynovitis by ultrasound in RA patients, ankle swelling being a superior predictive factor.
- Taking into account the information provided by ultrasound evaluation of the ankles of RA patients, we consider that the routine use of this imaging method should be encouraged, regardless of the presence of symptoms in the ankle, but this is possible only after standardization of an ankle evaluation protocol, which should include the STJ and the lateral and medial sections of the TTJ (to increase PD sensitivity).
- To reflect the current clinical reality of RA patients, a new DAS is needed to include clinical evaluation of the ankles, taking into account the information obtained by ultrasound evaluation, useful information for both clinical judgment (by more accurate identification of the extent of the inflammatory process), as well as for the therapeutic decision (local administration of glucocorticoids).

7. **Originality of the thesis**

The doctoral thesis brings new information about the evaluation of inflammation in the ankle of RA patients, both clinically and especially by ultrasound.

First, the data obtained from the analysis of this study are statistically relevant, the study sample being representative, both in number of patients (n = 183) and clinical spectrum of disease activity (including patients with and without ankle symptoms, respectively with and without RA activity, with early and constituted RA).

Second, unlike other cited studies, the ultrasound examination protocol also included the hindfoot, with the assessment of the posterior recess of the TTJ, as well as the assessment of the STJ in three sections (antero-medial, postero-medial and posterior) knowing that, regarding this last joint, the data from the literature are very few, incomplete, and its evaluation protocol is not standardized yet. In addition, to increase the accuracy of the comparison between ultrasound and MRI at the ankle, we tried to differentiate FC from SH, not only at the intra-articular level, but also in the tendon sheath (at this level, being the only study that evaluated FC and SH differently).

Third, it is the only study that evaluated the ankle of healthy subjects comparatively by two imaging methods, ultrasound and MRI, in order to identify physiological changes, in order to later define pathological changes at this level in RA patients. Defining the normal is the first step necessary for any imaging investigation protocol, being necessary in the case of ultrasound evaluation of the ankle, a need that this study fulfills.

Fourth, it is the only study that focused on the evaluation of the ankle in RA patients in remission, the results obtained emphasizing the need for clinical and ultrasound screening of

the ankles in this category of patients, taking into account the destructive potential of RA that determines, especially at this level, a severe functional deficit.

Fifth, the current study evaluated the predictive ability of the clinical examination for ultrasound-detected inflammatory lesions, separately, for pain and swelling of the ankle, respectively, thus observing that ankle swelling is a better predictive factor, both for ultrasound detection of intra-articular synovitis and for ultrasound detection of tenosynovitis in the ankle. The information is very valuable for the clinician, especially in the absence of access to ultrasound, as it allows him to adopt a therapeutic strategy appropriate to the actual activity of the disease.

Last but not least, it is the only study that managed to identify a cause for ultrasound-type inflammatory changes in the ankle, not only locally but also systemically, highlighting a direct proportional relationship between synovitis and tenosynovitis in the ankle and RA activity, emphasizing once again the importance of ankle evaluation in current medical practice, the clinical examination being supplemented by ultrasound evaluation.

In our opinion, the study makes a significant contribution by revealing further knowledge about the contribution of ultrasound information obtained from the examination of the ankles to the assessment of the degree of RA activity.

8. **Future research directions**

- ultrasound/MRI evaluation of the ankle, in healthy subjects, in a representative study sample, including bilateral imaging evaluation of the ankle, in order to analyze, in addition, the symmetry of the changes;
- evaluation of the prognosis of the persistence of inflammatory ultrasound lesions in the ankle in RA patients in remission, in terms of the risk of exacerbation of the disease (loss of remission);
- follow-up of patients with RA in remission, who have residual activity detected by ultrasound, in order to assess radiological progression;
- evaluating the usefulness and feasibility of ultrasound screening of the ankles in RA patients in remission, with the ultimate goal of achieving remission of inflammation in the ankle.

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