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# ABBREVIATIONS

| | |
|---|---|
| **ACPA** | Anti–citrullinated protein antibody |
| **ACR** | American College of Rheumatology |
| **AR** | Artrite Reumatóide |
| **CR** | Conventional Radiographic |
| **DAS-28** | Disease Activity Score (28 joints) |
| **D-MRI** | Dynamic Magnetic Resonance Imaging |
| **DMARD** | Disease Modifying Anti-Rheumatic Drugs |
| **EER** | Early Enhancement Rate |
| **ERA** | Early Rheumatoid Arthritis |
| **EULAR** | European League Against Rheumatism |
| **Gd-DTPA** | Gadolinium–diethylenetriamine Pentacetic Acid |
| **GSUS** | Grayscale Ultrasound |
| **HLA** | Human Leukocyte-Antigen |
| **MRI** | Magnetic Resonance Imaging |
| **OMERACT** | Outcome Measures in Rheumatology Clinical Trials |
| **OR** | Odds Ratio |
| **P-DUS** | Power Doppler Ultrasound |
| **RA** | Rheumatoid Arthritis |
| **RAMRIS** | Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System |
| **RE** | Relative Enhancement |
| **REE** | Rate of Early Enhancement |
| **RF** | Rheumatoid Factors |
| **SE** | Shared Epitope |
| **3D** | Three-dimensional |
| **UA** | Undifferentiated Arthritis |
| **US** | Ultrasound |
| **VdHmSS** | Van der Heijde Modified Sharp Score |
| **VERA** | Very Early Rheumatoid Arthritis |
| **VIBE** | Volumetric Interpolated Breath-Hold |

# *SUMMARY* [1]

The aim of this thesis was to identify the impact that newer imaging modalities namely Power Doppler ultrasound (P-DUS) and Dynamic Magnetic Resonance Imaging (D-MRI) have on the identification of individuals with early undifferentiated arthritis who eventually evolve to rheumatoid arthritis (RA).

In the Part I of our thesis we used a D-MRI protocol directed to both wrists and hands that included a volumetric interpolated breath-hold (VIBE) sequence with nearly isotropic resolution. We found that relative enhancement (RE), rate of early enhancement (REE), and Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) score for synovitis were significantly correlated with the disease activity score with 28 joint count (DAS28), suggesting that these parameters, even in early disease, can reflect the actual state of joint inflammation and disease activity.

In the part II of our thesis tenosynovitis of the extensor carpi ulnaris and of the flexor tendons of the second finger, in addition to radiocarpal joint synovitis, were recognised as significantly associated with progression to RA in patients with arthritis for less than 3 month's duration. Joint asymmetry rates of three quarters in very early RA (VERA) patients and two thirds in early RA (ERA) patients were detected, providing a morphological confirmation that early RA may be an asymmetrical disease and highlighting the relevance of a bilateral imaging protocol.

In the part III of our study we compared P-DUS and MRI findings of synovial inflammation using a bilateral hand and wrist evaluation. We identified a significant higher prevalence of synovitis by MRI. We also demonstrated a significant better diagnostic performance of 3-T MRI in comparison to US for RA diagnosis. If we took into consideration the group of patients with US joint and tendon count ≤ 10, the American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) criteria diagnostic performance was significantly improved by correcting clinical joint counts

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[1] Up to 300 in accordance with the 41st Article of the DR nº209, II Series, 30th October 2006.

with MRI joint and tendon counts. Our findings suggest that there is a specific subset of patients that can benefit from MRI joint and tendon counts.

Our results allow us to state that bilateral US and MRI evaluation of the hands and wrists in early arthritis can contribute for the early identification of RA patients. Identifying individuals at high risk of developing RA as soon and as precisely as possible is known as critical for the initiation of appropriate anti-rheumatic therapy.

# *SUMÁRIO* [1]

O objectivo desta tese foi identificar o impacto que novas técnicas de imagiologia, como a Ecografia Doppler (ECO-D) e a Ressonância Magnética Dinâmica (RM-D) podem ter na identificação de indivíduos que desenvolvem artrite reumatóide (AR), entre os que se apresentam com artrite indiferenciada precoce.

Na parte I desta tese utilizámos um protocolo de RM-D que incluiu uma sequência volumétrica interpolada (VIBE), com resolução quase isotrópica. Identificámos que a captação tardia, o índice de captação tardia e o score RAMRIS para sinovite encontram-se significativamente correlacionados com o score DAS28, sugerindo que estes parâmetros, mesmo em fase precoce da doença, podem refletir o grau atual de inflamação e de atividade da doença.

Na parte II desta tese a tenossinovite do extensor ulnar do carpo, dos tendões flexores do segundo dedo e da articulação radio-cárpica, foram reconhecidos como estando significativamente associados à progressão para AR em doentes com artrite de menos de 3 meses de duração. No nosso estudo bilateral foi detectada uma prevalência de assimetria de 80% nos doentes muito precoces e de 69.3% nos doentes precoces, fornecendo uma confirmação morfológica de que a AR pode ser uma doença assimétrica na fase inicial e salientando a importância de um protocolo de aquisição bilateral.

Na parte III do nosso estudo comparámos os achados de inflamação sinovial em ECO-D e RM utilizando uma avaliação bilateral das mãos e punhos. Identificámos uma prevalência significativamente superior de sinovite por RM. Igualmente demonstrámos uma performance diagnóstica significativamente superior da RM em 3-T quando comparada com a Eco para o diagnóstico de AR. Se tomarmos em consideração o grupo de doentes com contagem articular e tendinosa em ecografia ≤ 10, verificamos que a performance dos critérios ACR/EULAR fica significativamente melhorada, se substituída

[1] Resumo até 300 palavras de acordo com o Art.º 41º do DR nº209, II Série de 30 de Outubro de 2006.

a contagem clínica pela contagem em RM. Os nossos achados sugerem assim que existe um subgrupo específico de doentes que pode beneficiar da contagem articular e tendinosa por RM.

Os nossos resultados permitem afirmar que a avaliação bilateral das mãos e punhos por Eco e RM na artrite inicial podem contribuir para a identificação precoce de doentes com AR. A identificação de indivíduos em risco de desenvolver AR tão precocemente quanto possível é reconhecidamente um factor crítico para início de terapêutica anti-reumática apropriada.

# INTRODUCTION

# EARLY RHEUMATOID ARTHRITIS

## Pathophysiology

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disorder causing symmetrical polyarthritis of large and small joints, typically presenting between the ages of 30 to 50 years [1]. RA is the most common inflammatory chronic arthritis and afflicts 25 men and 54 women per 100,000 population [1-3]. There are differences in prevalence rates in RA in various ethnic groups, ranging from 0.1% in rural Africans to 5% in Pima or Chippewa Indians [4].

Rheumatoid arthritis pathogenesis involves a complex interplay among genotype and environmental triggers. Twin studies implicate genetic factors in rheumatoid arthritis, with concordance rates of 15 to 30% among monozygotic twins and 5% among dizygotic twins [5]. The long-established association with the human leukocyte-antigen HLA–DRB1 locus was confirmed by genome-wide association studies [6,7] and some predisposing T-cell repertoire selection, antigen presentation, or alteration in peptide affinity has a role in promoting autoreactive adaptive immune responses. Other possible explanations for the link between rheumatoid arthritis and the shared epitope (SE) include molecular mimicry of the SE by microbial proteins, increased T-cell senescence induced by SE–containing HLA molecules, and a potential pro-inflammatory signaling function unrelated to the role of the SE in antigen recognition [7-9].

Infectious agents (e.g., Epstein–Barr virus, cytomegalovirus, proteus species, and Escherichia coli) and their products (e.g., heat-shock proteins) have long been linked with rheumatoid arthritis, and although unifying mechanisms remain elusive, some form of molecular mimicry is postulated. The formation of immune complexes during infection may trigger the induction of rheumatoid factor (RF), a high-affinity autoantibody against the Fc portion of immunoglobulin, which has long served as a diagnostic marker for rheumatoid arthritis and is implicated in its pathogenesis [7]. The search for an etiologic agent has been unrewarding in respect to bacteria and their products although bacterial DNA is present in synovial tissue by sensitive polymerase chain reaction technique; however the species are not unique and have also been identified in many other arthropaties [10-11].

Studies of gene–environment interactions suggest that smoking and other forms of bronchial stress (e.g., exposure to silica) increase the risk of rheumatoid arthritis among subjects with susceptibility HLA–DR4 alleles [12]. Moreover, smoking and HLA-DRB1 alleles synergistically increase one's risk of having anti-citrullinated protein antibody (ACPA). In fact cigarette smoke is one of the best characterized environmental factors that increase the risk of RA [4].

The greater risk of rheumatoid arthritis among women has long been recognized. Women are two to three times more likely to develop RA than men. Hormonal factors like estrogen and progesterone could potentially explain some of the gender effect. The onset of rheumatoid arthritis is also associated with adverse life events. Molecular explanations for such phenomena are emerging from animal models [13].

The pathology of early and very early rheumatoid arthritis may be different from established disease. In the first 3 months after the onset of symptoms there is a distinct and temporally transient phase of the disease, characterized by a cytokine profile that is different from that in established RA and other very early synovitides [14]. The role of these characteristic cytokines in early RA is unclear but certain cytokines (e.g. fibroblast growth factor and epidermal growth factor) may contribute to the expansion of the stromal network that mediates the persistence of inflammation and drives joint destruction. Other cytokines (e.g. IL-2, -15, G-CSF and GM-CSF) may inhibit leucocyte apoptosis which is a characteristic of the very early rheumatoid lesion [15]. In addition, a number of chemokines [CCL2 (MCP1), CCL3 (MIP1-a), CCL4 (MIP1-b) and CCL5 (RANTES)] were identified in the very early rheumatoid lesion that may contribute to the recruitment of monocytes and lymphocytes [14].

Antibodies directed against joint-specific and systemic autoantigens are commonly detected in the blood of RA patients. RF are autoantibodies directed against the Fc portion of IgG. IgG and IgM RF test positive in about 50% of cases at presentation and an additional 20-35% of cases become positive in the first 6 months after diagnosis.

However, these autoantibodies can also be produced during chronic infections, malignancy, and in a variety of inflammatory and autoimmune disorders. ACPA are another key autoantibody in RA. ACPA testing has a sensitivity of up to 80% to 90% and a specificity of 95% for RA. Autoantibodies are also found in immune complex deposits in rheumatoid joints and synovial tissue and might contribute to local inflammation by activating complement [16, 17].

The synovium is the primary site of inflammation in RA. Synovitis occurs when leukocytes infiltrate the synovial compartment. Leukocyte accumulation primarily reflects migration rather than local proliferation. Cell migration is enabled by endothelial activation in synovial microvessels, which increases the expression of adhesion molecules (including integrins, selectins, and members of the immunoglobulin superfamily) and chemokines. Accordingly, neoangiogenesis, which is induced by local hypoxic conditions and cytokines, and insufficient lymphangiogenesis, are characteristic features of early and established synovitis. Increased numbers of both type A and B synoviocites augment the depth of the lining layer and mononuclear cells infiltrate the sub-layer. These microenvironmental changes, combined with profound synovial architectural reorganization and local fibroblast activation, allow the buildup of synovial inflammatory tissue in rheumatoid arthritis [18].

## Clinical Findings

The typical clinical presentation of RA is polyarticular, with pain, stiffness, and swelling of multiple joints in a bilateral, symmetric pattern. However, it may be asymmetrical and oligoarticular in some cases, particularly at early disease stages [19]. Patients who have asymmetrical joint involvement have a tendency for the less affected site to undergo increased damage (symmetrization). The literature varies with regard to the prevalence of asymmetry, which is reported to range from 12% to 94%, depending on the stage of disease and how asymmetry is defined. Asymmetrical presentation has been found to become symmetric with advanced disease and a change from asymmetry to symmetry within 1 year was shown to predict more severe disease [20-25].

The onset is usually insidious, with joint symptoms emerging over weeks-months and often accompanied by anorexia, weakness, or fatigue. Patients usually note morning stiffness lasting more than one hour. Commonly involved joints are the wrists, proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints, with distal interphalangeal joints and spinal joints usually spared. Typical examination findings include swelling, tenderness and warmth. The hands are a major site of involvement in almost all patients with RA and hand involvement is responsible for a significant proportion of the disability caused by the disease. Extra-articular manifestations tend to be more common in those patients with RF and include rheumatoid nodules, small vessel vasculitis, pyoderma gangrenosum, coronary artery disease, pericardial effusions, pleural effusions, pulmonary rheumatoid nodules, diffuse interstitial fibrosis, keratoconjunctivitis sicca, scleritis, peripheral nerve entrapment syndromes and Felty syndrome [26].

### Diagnosis

There is no single clinical manifestation, laboratory test, or imaging study result that allows a definitive diagnosis of RA [27]. Radiographs are generally not helpful for early diagnosis, as fewer than 20–25% of patients have erosions initially; furthermore, up to 30% of patients test negative for serum rheumatoid factor (RF), and other pathognomonic features such as rheumatoid nodules usually appear late in the disease process [28-30].

X-ray is the traditional gold standard for assessment of joint damage in RA. Bone erosions, joint space narrowing as an indirect sign of cartilage thinning, juxta-articular osteoporosis, cysts and, in severe cases, joint subluxations, malalignment or ankylosis can be demonstrated on established RA [31, 32]. X-ray depicts the time-integrated cumulative record of joint damage. Its advantages are low costs, high availability, possibility of standardization and blinded centralized reading, reasonable reproducibility, and existence of validated assessment methods [33, 34]. Disadvantages of X-ray include projectional superimposition due to two dimensional representation of three-dimensional pathology, use of ionizing radiation, insensitivity to early bone damage, and total insufficiency for assessment of soft tissue changes including synovitis [35-37]. Early bone erosions in RA are correlated with poor long-term radiographical and functional outcome [38], and in early undifferentiated arthritis, presence of X-ray erosion increases the risk of developing persistent arthritis. [39] However, radiographic erosions are only present in a minority of patients with early RA, with prevalences of 8–40% at 6 months [40-43], and X-ray is not effective for identifying future 'non-progressors', i.e. patients that will not show increasing structural joint damage. [44] In routine clinical management and clinical trials, X-ray evaluation focuses on joint space narrowing and bone erosions which are features of established disease [45, 46]. In early disease, X-ray status is not related to functional outcome measures like the Health Assessment Questionnaire (HAQ) score, while in established disease (5–8 years of disease duration), the radiographical damage and functional status are significantly correlated (correlation coefficient 0.3–0.5) [47]. It is likely that more advanced imaging modalities, could provide a more sensitive evaluation in early disease.

The RF test is used as a diagnostic marker for rheumatoid arthritis, since its presence is associated with an increased risk of developing RA in people with arthritic symptoms. Higher levels are also detected in more severe forms of the disease, a condition that has prognostic relevance. However, RF is also detected in other diseases as well as in healthy individuals, especially in the elderly, thus lowering its specificity [48, 49]. The amount of RF in blood can be measured by nephelometric test by latex particle agglutination assay. This technique is widely used in clinical laboratories because of its relatively easy automation. The principle of this methodology relies on the use of polystyrene (latex) particles coated with an immuno-complex, consisting of human γ-globulin/anti-human γ-globulins from sheep. The patient blood is mixed with beads and agglutinates in the presence of RF. The agglutination reaction is measured by a nephelometer [50]. Nowadays, many autoimmunity laboratories have adopted analytic platforms, such as enzyme linked immunoassays (ELISA) [51].

Citrullination, or peptidylarginine deimination, is the process by which the imino group of the guanidine moiety of arginine is hydrolysed, leading to the replacement of the protonated imino group by an oxygen atom. In this way citrulline is a nonstandard amino acid, that is not incorporated into proteins during protein synthesis; it is incorporated via the posttranslational modification of arginine residues [52]. The process is generally catalysed by a specific enzyme, the peptidylarginine deaminase. A biochemical ELISA test was developed by Walther van Venrooij and colleagues [53] to detect ACPA in sera of RA patients. It has been reported that the presence of ACPA predicts a more aggressive course of disease with unfavorable outcome [54-56]. Importantly, ACPA are present early in disease. There is convincing evidence [57, 58] from serum samples from RA patients that were collected when these patients were still healthy that the ACPA are present before disease onset. The predictive potential of a positive ACPA is a great advantage, especially in early arthritis [59]. Van Gaalen et al. [60] reported that ACPA positivity could be used to identify a subset of patients with undifferentiated arthritis that would progress to RA in 3 years. The observations that ACPA are often detected years before the disease becomes manifest [57, 58] with increasing titers as patients approach disease onset [61, 62], suggest that the initial trigger for the development of RA may occur long before the appearance of symptoms. Even so, a recent study by Narvaez et al. [63] suggest that although the tests are not mutually exclusive, MRI could be more helpful than ACPA determination in confirming the diagnosis of clinically suspected early RA in patients in whom the diagnosis cannot be confirmed using conventional methods.

The 1987 revised criteria for RA of the American College of Rheumatology (ACR; formerly the American Rheumatism Association) [64], were not designed specifically for the purpose of diagnosis (originally intended for use in epidemiological studies and clinical trials), and have limited value (low sensitivity and specificity) for early arthritis. The new 2010 RA ACR/EULAR classification criteria [65] emphasized the identification of patients with a relatively short duration of symptoms. However, while the new criteria are better than the 1987 criteria for early identification of patients requiring disease-modifying anti-rheumatic drugs (DMARD) [66], a recent study with a very early inflammatory arthritis cohort highlighted that they may lead to significant over- and under-diagnosis if used to direct treatment within the first 3 months after the onset of symptoms, the phase when treatment makes a greater difference [67] and may miss patients with symmetrical seronegative arthritis and limited joint involvement [68]. The 2010 ACR/EULAR classification criteria already consider evidence of joint activity from imaging techniques (such as magnetic resonance imaging or ultrasound) for the purpose of quantification of “joint involvement” and score calculation [65]. However, the details of this contribution from imaging techniques and their impact in terms of diagnostic capability remain largely unknown.

### Therapeutic Strategy

Early consideration of DMARD therapy is essential whenever RA is suspected and became a crucial aspect of RA management [69-75]. Early DMARD therapy is consistently associated with lower disease activity measures, a greater likelihood of achieving clinical remission [76, 77], reduced radiographic progression rates [78], lower levels of long-term functional and work disability [79] and lower mortality rates [80]. This focus on earlier and potentially modifiable disease suggests the possibility of a therapeutic window of opportunity, a period of disease onset or course wherein appropriate intervention yields the greatest impact on disease progression.

However, therapeutic decisions are hindered by the already mentioned non-specific early clinical features of RA.

Therefore, the use of additional tests, namely more sensitive imaging techniques, would be helpful to address this diagnostic problem.

An increased number of capillaries have been observed in the RA synovial membrane as compared with the normal synovial membrane. In addition, the inflammatory process enhances capillary perfusion and permeability. Increased vascularization fosters the trafficking of antigens and cells to the sites of inflammation and the production of adhesion molecules in the vessel wall. The synovial cells receive abundant nutrients and proliferate to form the rheumatoid pannus. These considerations indicate that evaluating the synovial vascular bed could be a valuable method to diagnose early-phase RA and follow its course [81-84].

Gadolinium–diethylenetriamine pentacetic acid (Gd-DTPA), a paramagnetic contrast agent, is transported in the plasma as an unlinked molecule and diffuses freely to the interstitial space. It allows differentiation of the synovial membrane from the surrounding tissues through a marked increase of signal intensity on T1-weighted images [81]. Its diffusion and pharmacokinetics are influenced by several determinants. Blood pressure, cardiac rate and intra-articular pressure due to fluid effusion are unpredictable variables that may affect the results of dynamic enhancement but can hardly be standardized. Standardization of the infusion technique is crucial with respect to the quantity of Gd-DTPA injected according to the patient´s weight and the duration of infusion. D-MRI has been proposed as an imaging modality for the estimation of inflammation in established RA. D-MRI consists of a fast repeated series of volumetric interpolated breath old sequences (VIBE) or other three-dimensional (3D) spoiled gradient-echo images. The VIBE sequence is a modified fast 3D gradient-echo sequence that provides isotropic or nearly isotropic resolution in three dimensions while preserving wide anatomic coverage in a short acquisition time; motion artifacts are also reduced by the rapid data acquisition time [82]. The sequences usually cover the enhancement during the first 4 post contrast minutes. The acquisition time depends on the possibility of acquiring only one sequence with isotropic pixels and obtaining secondary reconstructions of high quality in other plane [83]. The synovial enhancement curves are generally analysed with two major parameters: the early enhancement rate (EER) that has been used in most studies and measured over various intervals ranging from 10 to 60 seconds [83, 84] and the relative enhancement (RE) that peaks 1.5 minutes after Gd-DTPA injection. During this period enhancement provides more detailed information on the inflammatory activity of the synovial membrane than data obtained on late images, where the curves reach a plateau. EER has a complex dependence on multiple underlying physiological parameters due to the cumulative effects of the plasma fractional volume of vessels within the synovium, the volume transfer constant reflecting the vascular parietal permeability, the fractional extravascular, extracellular fluid volume, and the T1 relaxation rate of the synovium [84]. EER of the total synovial membrane of a preselected slice is highly correlated with histologic features of active inflammation, particularly vessel proliferation (angiogenesis) and mononuclear leucocyte infiltration. Dynamic MRI with variation of EER (EER ≥ 1%/sec) is able to distinguish joints with and without synovial inflammation, so patients with active RA or those who are in remission or control with a high predictive value but moderate or severe inflammation (different levels of disease activity) can be differentiated [84, 85, 86]. EER and RE measurements in wrist and MCP joints are both significantly correlated with the number of swollen joints and tender joints, Ritchie index, Disease activity score, early morning stiffness, C-reactive protein level, and erythrocyte sedimentation rate, and thus are relevant for discriminating active from inactive RA [87]. EER decreases after treatment (steroids, disease modifying and anti-TNF drugs) with responses demonstrated as early as 1 to 2 weeks after starting treatment [84, 88, 89]. The study by Cimmino et al. [90] focusing in established RA, studied 36 patients and 5 healthy controls (0.2 T, one hand and wrist, laterality not specified). The curves of synovial membrane enhancement identified the following 2 groups: controls and RA patients in remission, and RA patients with active or intermediately active disease. Both the rate of early enhancement (REE) and relative enhancement (RE) were significantly higher in patients with active RA than in those with inactive RA and controls. The REE and RE were significantly correlated with the number of swollen joints, the number of tender joints, the disease activity score and the health assessment questionnaire, early morning stiffness, the C-reactive protein level and the erythrocyte sedimentation rate. Another work from the same author [91] demonstrated that dynamic MRI shows the same pattern of synovitis in patients with psoriatic arthritis and RA when the two groups are matched for disease severity. This may suggest that the amount of contrast agent transported to the inflamed synovial membrane is probably a result of the number, size and permeability of the vessels and volume of the synovial membrane itself.

MRI is a highly sensitive method for detecting early inflammatory and structural abnormalities in RA joints [91-98]. Synovitis is the earliest abnormality to appear in RA. The synovial tissue that lines normal cavities, bursae and tendinous sheats can be detected by MRI owing to increased synovial volume, increased water content and contrast enhancement [99-102]. Synovitis has been shown to enhance rapidly and intensely after the intravenous administration of gadolinium-based contrast material unlike joint effusion which does not enhance in the early phase. This early phase lasts for approximately 3 minutes after injection. Images that are obtained later may not accurately delineate the extent of the synovitis, since gadolinium may diffuse into the synovial joint fluid [103].

MR imaging has been shown to be more sensitive than clinical examination for the detection of synovitis in patients with rheumatoid arthritis [104, 105]. MR imaging detection of synovitis has prognostic value for the subsequent appearance of erosions during follow-up [104-106].

Fibrotic pannus, which is usually present in end-stage rheumatoid arthritis, appears relatively hypovascular after the intravenous administration of gadolinium-based contrast material. Moreover, with T2-weighted sequences, fibrous pannus with intermediate to low signal intensity can be distinguished from acute synovitis and joint fluid [99, 101].

The volume of inflamed synovium can be quantified on contrast-enhanced MR images with use of manual or semiautomated methods. Quantitative assessment of synovitis is favored owing to its higher accuracy and may be considered the standard of reference, but it is very time consuming and is usually reserved for clinical trials or other research studies [102, 103]. Semi-quantitative scoring methods for evaluating synovial volume are also based on assessment of the amount of enhancing synovium [104, 105, 109]. These methods are considerably faster than quantitative measures and may be applied when less than complete information is needed, since a relatively close correlation has been found [110]. Several studies have described the scoring of synovitis in early rheumatoid arthritis at MR imaging. With these methods, synovitis is graded either in the joint as a whole [109] or in several regions per joint [104, 105, 111]. The most frequently used method is the OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS), which allows assessment of synovitis in the following regions: distal radioulnar joint; radiocarpal joint; intercarpal and carpometacarpophalangeal, CMC, joints; metacarpophalangeal, MCP, joints; proximal interphalangeal, PIP, joints (excluding the 1st CMC, the 1st MCP and the 1st PIP). A score of 0 to 3 is assigned for each joint, where 0 is normal with no synovial enhancement and 3 the maximum presumed volume of enhancing tissue in the synovial compartment [112].

Haavardsholm et al. [113] demonstrated in a study enrolling 84 early RA patients treated according to standard clinical practice and with MRI evaluation (dominant wrist, 1.5 T) at baseline, 3, 6 and 12 months, that MRI findings reflecting inflammation (synovitis, bone marrow oedema and tenosynovitis) decreased during follow-up and that there was a small increase in MRI erosion score. Baseline MRI bone marrow oedema was identified as an independent predictor of both conventional radiographic (CR) damage (OR = 2.77) and MRI erosive progression (B = 0.21). The study by Narvaez et al. [114] included 40 patients with early inflammatory arthritis and strong clinical suspicion of RA, in whom initial complementary tests did not provide unequivocal confirmation of the diagnosis. Use of MRI (most affected hand, 1.5T) criterion led to the correct diagnosis in 100% of patients that developed RA at the 1 year follow-up. The MRI criterion had a specificity of 78% and sensitivity of 100% for identification of seronegative RA. Boutry et al. [115] obtained an MRI examination of the hands and feet of 30 early RA patients (1.5 T, both hands). In the hands, MRI findings suggested active synovitis of the wrist and metacarpophalangeal joints in 28 (93%) and 27 (90%) patients, respectively. MRI detected tenosynovitis in 16 (53%) patients in the hands. The most common sites for tendon involvement were the flexor digitorum, extensor digitorum, extensor carpi ulnaris and extensor carpi radialis. Another study by Boutry et al. [116] prospectively evaluated the use of MRI (1.5 T, both hands) for differentiating early RA from systemic lupus erythematosus (SLE) or primary Sjogren syndrome in patients with inflammatory arthralgia of the hands but no radiographic evidence of RA. Synovitis and tenosynovitis were identified in 100% and 96% of patients respectively (wrists joints) and 100% and 68% of patients respectively (MCP joints).

Tenosynovitis is a common problem in rheumatoid arthritis (RA), and is observed in a large proportion of these patients. [117, 118] It is not specific for RA, and has also been described in other rheumatological diseases, such as systemic lupus erythematosus [119]. The tenosynovium produces proinflammatory cytokines and proteolytic enzymes that are important in the tissue degradation seen in RA [120]. The proliferation of the tenosynovial lining can lead to impaired function due to scarring and adhesions. Flexor tenosynovitis in the hands has also been identified as a risk factor for destructive erosion of the joints [121]. The ongoing tenosynovial inflammation may ultimately lead to tendon rupture, which is a serious complication that leads to reduced hand function [122]. Haavardsholm et al [123] described a method for semi-quantitative grading of tendon sheath abnormalities from grade 0 to grade 3, reflecting the maximum width (in mm) of enhancement within each anatomical area as described: Grade 0 (normal): no peritendinous effusion or synovial proliferation with enhancement; Grade 1: < 2 mm peritendinous effusion and/or synovial proliferation with enhancement; Grade 2: >2 and < 5 mm peritendinous effusion and/or synovial proliferation with enhancement; Grade 3: >5 mm peritendinous effusion and/or synovial proliferation with enhancement.

However tenosynovitis of the wrists and hands has been relatively neglected in the rheumatology literature, particularly in early disease stages, receiving far less attention than synovitis, erosions, bone marrow oedema, and other MR imaging findings characteristic of early rheumatoid arthritis. One recent report by Eshed et al. identified flexor tenosynovitis diagnosed by MRI of the hand as the most powerful MRI predictor of early rheumatoid arthritis (sensitivity = 60%, specificity = 73%) [124]; the work included 99 patients, of which 58 had a clinical diagnosis of RA and 41 were diagnosed as non-RA. However the study was performed with an extremely low field-strength extremity MRI unit (0.2 Tesla), which limits the sensitivity of the evaluation, and included patients with disease duration up to 24 months, encompassing most of the currently accepted definitions of early RA [125, 126]. The work by McQueen at al. [127] studied the occurrence, pattern and progression of tendinopathy by hand and wrist MRI over 6 years in a cohort of 42 patients who had presented with early RA. The most common affected site was the extensor carpi ulnaris. Lillegraven et al [128] evaluated a cohort of 60 early RA patients by MRI and ultrasonography at 0, 12 and 36 months. They have found that extensor carpi ulnaris was a statistically significant univariate predictor of 3-year progression of RAMRIS erosion score (OR = 3.4), and was a borderline significant predictor of 1-year progression in vdHmSS erosion score (OR = 2.85) and total vdHmSS (OR = 2.50) in univariate analysis.

Previous studies showed correlation between D-MRI parameters and clinical findings and treatment effects. However, all these studies were performed with low-field MRI using quite complex formulae for enhancement quantification and were performed in patients with established RA. Besides, the knee and wrist have been most commonly assessed. In this way, D-MRI parameters of hands and wrist inflammation in early arthritis patients at high field strength MRI are still largely unknown. The way in which bilateral hands and wrist high field-strength MRI detection of tenosynovitis, combined with detection of joint synovitis, could contribute for the discrimination of early arthritis patients with high probability of developing RA is also a clinical and scientific unmet need.

The generation of new blood vessels is required to provide nutrients to the expanding synovial membrane and angiogenesis is greatly stimulated in RA [129-133]. P-DUS, by providing information on blood flow, independently of imaging angle, flow direction and velocity, displaying the integrated power of the Doppler signal [134], can provide a measurement of synovial increased vascularity and inflammation.

P-DUS estimates the degree of synovial inflammation. Changes in the degree of activity of the inflammatory process may be determined according to changes in the amount of color pixels in the region of interest [134]. Thickening of the synovial membrane of inflamed joints, bursae, or tendon sheats, can also be detected by B-mode ultrasound [135].

Musculoskeletal ultrasound has been demonstrated to be more sensitive than clinical assessment in the detection of joint synovitis [136, 137] and more sensitive than conventional radiography in the detection of erosions [138]. Investigators have recently explored the use of restricted ultrasound joint counts to predict persistent inflammatory arthritis in symptomatic patients with hand synovitis or arthralgia presenting in the first 3 months of disease [139]. A number of scoring systems have been developed [140-152], all methods involving some degree of subjectivity, since no automated or semi-automated system for quantification have been introduced. One of the semi-quantitative used systems is the one proposed by Szkudlarek, et al [144] which defined synovitis as a noncompressible hypoechoic intracapsular area (synovial thickening): 0 - no synovial thickening; 1 - minimal synovial thickening (filling the angle between the periarticular bones, without bulging over the line linking tops of the bones), 2 – synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis; 3 - synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses. Power Doppler signal was defined as: 0 - no flow in the synovium; 1 - single vessel signals; 2 - confluent vessel signals in less than half of the area of the synovium; 3 - vessel signals in more than half of the area of the synovium.

At the 7th OMERACT conference (Outcome Measurement Rheumatoid Arthritis Clinical Trial), definitions of sonographic abnormalities were also set in order to standardize the ultrasound assessment of early arthritis patients [153]. The following definitions were accepted: Synovial fluid - abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular material that is displaceable and compressible, but does not exhibit Doppler signal; Synovial Hypertrophy - abnormal hypoechoic (relative to subdermal fat, but sometimes isoechoic or hyperechoic) intra-articular tissue that is non-displaceable and poorly compressible, which may exhibit Doppler signal; Tenosynovitis - hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and may exhibit Doppler signal; Enthesopathy - abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci of calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity; Rheumatoid arthritis bone erosion - an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes.

The recent work by Filer at al. [154] enrolled 58 patients with clinically apparent synovitis of at least one joint and symptom duration of ≤ 3 months (very early RA) that were followed prospectively for 18 months determining outcome by the 1987 ACR and 2010 ACR/EULAR criteria, demonstrated that ultrasound identified subclinical synovitis in patients developing RA; regression analysis demonstrated that grayscale wrist and metacarpophalangeal joint involvement provided independent predictive data. The study by Salaffi et al. [155] confirmed that clinical examination is far from optimal for assessing joint inflammation in patients with early RA and that US can considerably improve the detection of signs of joint inflammation both in terms of sensitivity and reliability. In the work by Mendonca et al [156] 42 wrists were evaluated using semi-quantitative scales P-DUS and gray scale ultrasound (GSUS) and correlated with clinical, laboratory and radiographic data. Twenty-one patients were enrolled in the study, that showed significant correlations between clinical, sonographic and laboratory data: GSUS and swollen right wrist (r = 0.546), GSUS of right wrist and swelling of left wrist (r =

0.511), PDUS of right wrist and pain in left wrist (r = 0.436), PDUS of right wrist and C-reactive protein (r = 0.466). In the paper by Millot et al [157] involving 127 healthy subjects matched with a cohort of patients with early arthritis (the ESPOIR cohort), bone erosion and grade 2-3 synovial thickening in B-mode were detected in 11% and 9% of healthy subjects. A cutoff at 1 case of synovial thickening in B-mode enabled discrimination between patients with early arthritis and healthy subjects, with a good sensitivity of 74.8% (95% CI, 67.2%-82.3%) and a high specificity of 90.5% (95% CI, 85.4%-95.6%); more than 1 case of synovial thickening in B-mode or bone erosion is a strong argument for the diagnosis of early inflammatory arthritis. In a recent work by Salaffi et al. [158] 149 adult patients with recent-onset UA were submitted to P-DUS and the combination with routine assessment variables was investigated with the purpose of developing a prediction rule. The authors found that the inclusion of PDUS assessment in the rule, provided an excellent discriminative ability for assessing the likelihood of development of RA in patients with an early-onset UA. Freeston et al. [159] approached a cohort of patients with very early inflammatory arthritis that was followed for 12 months and were submitted to PDUS, clinical and laboratory evaluation. They have found that in seronegative patients (RF and CCP negative) group the addition of clinical and radiographic features raised the probability of inflammatory arthritis to 30% and, with certain ultrasound features, this rose to 94%, concluding that in seronegative patients with early inflammatory arthritis, combining PDUS with routine assessment can have a major impact on the certainty of diagnosis.

In this way, ultrasound is already known to have a better reliability in comparison to clinical indices for synovitis evaluation [160] and there is accumulating evidence of its usefulness for the diagnosis and monitoring of several rheumatic disorders [161]. However, US can be time consuming, has a long learning curve and is operator dependent [161, 162]. Magnetic resonance imaging provide a better morphologic characterization than US and is generally recognized as the non-invasive imaging modality of choice for visualisation of the inflamed synovium in established RA and is increasingly being used in the assessment of early RA [163]. Nonetheless, MRI poses financial constraints, requires a larger period of time for the examination than US and sometimes needs the administration of an EV contrast agent [162].

In this way the comparative evaluation of the diagnostic performance and determination of the added value of each technique could have a critical role in patient management. Studies comparing the diagnostic performance of US with MRI in early arthritis have been focused only on the dominant or the clinically most affected hand, with alternative study of joint or tendon disease and have used a low magnetic field (less than 1.5 Tesla)  [164-166]. These limitations may have hindered an adequate comparison of the performance of US and MRI in early RA. In fact, to the best of our knowledge, there is no reported comparison between Doppler US and 3-T MRI findings in early RA.

# AIMS

The aims of this thesis were to identify the impact that newer imaging modalities like P-DUS and D-MRI can have on early detection and monitoring of synovitis. It was also our objective to provide information that could be significant on the identification of individuals with undifferentiated arthritis who will develop RA.

The specific aims of this work are:

I. To identify factors with new imaging techniques, P-DUS and D-MRI, that predict progression to RA in patients presenting with early inflammatory arthropathy.

II. To compare the capacity of P-DUS and D-MRI in evaluating the degree of synovial inflammation.

III. To correlate the imaging data with patient clinical and laboratory characteristics.

# RESULTS

In agreement with the Decreto-Lei 388/70, art. 8º, the results presented and discussed in this thesis were published, accepted or submitted for publication in the following scientific peer-reviewed journals:

I. **Márcio Navalho**, Catarina Resende, Ana Maria Rodrigues, Augusto Gaspar, João Eurico Fonseca, Helena Canhão, Jorge Campos. Dynamic contrast-enhanced 3-T magnetic resonance imaging: a method for quantifying disease activity in early polyarthritis. *Skeletal Radiol 2012;41:51–59.*

II. **Márcio Navalho,** Catarina Resende, Ana Maria Rodrigues, Filipa Ramos, Augusto Gaspar, J Alberto Pereira da Silva, João Eurico Fonseca, Jorge Campos, Helena Canhão. Bilateral Magnetic Resonance Imaging of the Hand and Wrist in Early and Very Early Inflammatory Arthritis: Tenosynovitis is Associated with Progression to Rheumatoid Arthritis. *Radiology* 2012; doi:10.1148/radiol.12112513 *published online ahead of print*.

III. **Márcio Navalho**, Catarina Resende, Ana Maria Rodrigues, J Alberto Pereira da Silva, João Eurico Fonseca, Jorge Campos, Helena Canhão. Bilateral Evaluation of the Hand and Wrist in Untreated Early Inflammatory Arthritis: a Comparative study of Ultrasonography and Magnetic Resonance Imaging. *The Journal of Rheumatology 2012 – Submitted for publication*

# PART I

**Dynamic contrast-enhanced 3-T magnetic resonance imaging: a method for quantifying disease activity in early polyarthritis**

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SCIENTIFIC ARTICLE

# Dynamic contrast-enhanced 3-T magnetic resonance imaging: a method for quantifying disease activity in early polyarthritis

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**Abstract**

*Objective* To determine whether measurement of synovial enhancement and thickness quantification parameters with 3.0-Tesla magnetic resonance imaging (3-T MRI) can reliably quantify disease activity in patients with early polyarthritis.

*Materials and methods* Eighteen patients (16 women, 2 men; mean age 46 years) with early polyarthritis with less than 12 months of symptoms were included. MRI examination using 3-T device was performed by a new approach including both wrists and hands simultaneously in the examination field-of-view. MRI scoring of disease activity included quantification of synovial enhancement with simple measurements such as rate of early enhancement (REE; $REE_{57}=S_{57}/S_{200}$, where $S_{57}$ and $S_{200}$ are the signal intensities 57 s and 200 s after gadolinium injection) and rate of relative enhancement (RE; $RE=S_{200}-S_0$). Both wrists and hands were scored according to the Rheumatoid Arthritis MRI Scoring System (RAMRIS) for synovitis. Disease activity was clinically assessed by the 28-joint Disease Activity Score (DAS28).

*Results* DAS28 score was strongly correlated with RE ($r$= 0.8331, $p<0.0001$), REE ($r$=0.8112, $p<0.0001$), and RAMRIS score for synovitis ($r$=0.7659, $p$<0.0002). An REE score above 0.778 accurately identified patients with clinically active disease (sensitivity 92%; specificity 67%; $p$<0.05). A statistically significant difference was observed in the RE, REE, and RAMRIS scores for synovitis between patients with active and inactive disease ($p$<0.05).

*Conclusions* Our findings support the use of 3-T dynamic contrast-enhanced MRI for precise quantification of disease activity and for discriminating active disease from inactive disease in early polyarthritis.

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**Keywords** Early arthritis · Rheumatoid arthritis · Disease activity · Magnetic resonance imaging · Dynamic

## Introduction

Several studies have proposed synovial angiogenesis as one of the earliest markers of arthritis. The generation of new blood vessels is required to provide nutrients and inflammatory cells to the expanding synovial membrane [1, 2]. In addition, angiogenic cytokines, which also mediate changes in synovial permeability, are present in the synovial fluid and synovium of established rheumatoid arthritis (RA) patients [3, 4].

The enhanced synovial membrane observed in post-contrast magnetic resonance images represents highly vascularized inflamed synovial tissue. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), consisting of a fast-repeated series of image acquisition after contrast injection, allows the time course of synovial enhancement to be analyzed [5]; furthermore, the enhancement rate has been shown to correlate with histological parameters of angiogenesis and inflammation [6–9].

Previous studies showed correlation between DCE-MRI parameters and clinical findings and treatment effects [10–16]. However, all these studies were performed with low-field MRI using quite complex formulae for enhancement quantification and using patients with established RA. As well, the knee and wrist have been most commonly assessed; in the latter case, only the dominant hand was evaluated [1, 7, 10, 11, 13–29].

We hypothesized that the advantages of 3-T MRI, including greater field strength, increased signal-to-noise ratio, improved image quality, and decreased scan time, could make a difference not only in morphological analysis but also in display of dynamic curves. The enhancement rate in these conditions will probably be a direct function of the local degree of inflammation and a precise and simple measure of disease activity, even in patients with early polyarthritis.

Considering that the technique is known to provide a precise and complete morphological analysis of the hands and wrists [30], the possible benefit of obtaining functional information could make it an ideal candidate for long-term follow-up of patients.

Thus, the purpose of this work was to correlate simple 3-T MRI parameters of synovial enhancement with an extensively validated clinical index of disease activity, the 28-joint Disease Activity Score (DAS28) [31], in patients with early polyarthritis. We also intended to determine the correlation between morphological quantification of synovitis using the Rheumatoid Arthritis MRI Scoring System (RAMRIS) for synovitis [32] with DAS28 using our new approach of including both hands in the field-of-view (FOV) at high field strength, which allows precise evaluation. Finally, we aimed at identifying a cutoff value to obtain the most reproducible and reliable MRI measurement that identifies patients with clinically active disease.

## Materials and methods

### Patients

Eighteen patients with early polyarthritis involving the wrists and hands having less than 12 months of symptoms were included in the study. The patients were recruited from the rheumatology outpatient clinic of Hospital da Luz and Hospital de Santa Maria in Lisbon. There were 16 women and 2 men with a median age of 46 years (range 16–67 years).

The exclusion criteria included pregnancy or nursing; inability to give informed consent; current use of glucocorticoids, methotrexate, or other disease-modifying antirheumatic drugs (DMARDs); active malignancy, cellulitis, or osteomyelitis; and contraindications to performing an MRI.

All patients provided informed consent, and the ethical principles for medical research involving human subjects according to the World Medical Association Declaration of Helsinki were fulfilled. The study was approved by the local ethics committee.

Patients were clinically evaluated for a specific diagnosis at the time of MRI examination and after 6 and 12 months. Twelve patients were diagnosed with RA according to the 1987 American College of Rheumatology (formerly the American Rheumatism Association) criteria [33] and were retrospectively found to meet the 2010 RA classification criteria of the American College of Rheumatology/European

**Table 1** Demographic, clinical, and laboratory data of patients

| Characteristic | Patients ($n$=18) |
|---|---|
| Number (men/women) | 2/16 |
| Age (years) | 46.1±13.9 |
| Disease duration (months) | 6.2±3.0 |
| Tender joint count ($n$) | 7.1±5.2 |
| Swollen joint count ($n$) | 4.8±4.0 |
| ESR (mm/h) | 36.5±36.0 |
| Overall disease activity (VAS) | 56.8±23.4 |
| DAS28 | 4.8±1.7 |

Except where indicated, the values are mean±standard deviation (SD)
*ESR* Erythrocyte sedimentation rate, *VAS* visual analog scale, *DAS28* 28-joint disease activity score

**Table 2** Correlation between DAS28 and RE, EER, and RAMRIS score for synovitis

| Characteristic | Mean±SD ($n$=18) | Correlation with DAS28[a] | |
|---|---|---|---|
| | | Correlation coefficient (95% CI) | $p$ |
| RE | 733.8±314.0 | 0.8331 (0.5993–0.9360) | <0.0001 |
| REE | 0.80±0.14 | 0.8112 (0.5542–0.9270) | <0.0001 |
| RAMRIS for synovitis[b] | 8.9±9.3 | 0.7659 (0.4654–0.9081) | <0.0002 |

[a] Pearson's test

[b] The value corresponds to the sum of the score obtained for each hand (calculated as described by Lassere et al. [32]) because both the hands were included in the FOV

League Against Rheumatism [34]. Two patients were diagnosed with undifferentiated polyarthritis (after 12 months without criteria for specific diagnosis); 4 patients did not meet the criteria for specific diagnosis at the time of MRI examination and had not reached the 12-month clinical evaluation point.

The DAS28 clinical parameter components, such as the number of tender and swollen joints, the patient's overall disease activity on a visual analog scale, and erythrocyte sedimentation rate (ESR) were evaluated prior to MRI examination. Disease activity was assessed by calculating the DAS28 score for each patient [31].

## MRI evaluation

MRI examination of the wrist and hands was performed on a 3.0-T device (Siemens Magnetom Verio) by using a six-channel surface phased array body coil including both hands simultaneously in the FOV; patients were placed in the prone position with their hands side-by-side fixed over their head with the help of several cushions. The following sequences were acquired before intravenous injection: T1-weighted fast spin-echo sequences on the axial [FOV 230 mm, slice thickness (ST) 3.5 mm, repetition time (TR)/echo time (TE) 696/31 ms, matrix 384×384, turbo factor (TF) 4, slice number 45] and coronal planes (FOV 250 mm, ST 2.0 mm, TR/TE 583/21 ms, matrix 384×384, TF 4, slice number 24), proton density-weighted fast spin-echo sequence with fat saturation on the coronal plane (FOV 250 mm, ST 2.0 mm, TR/TE 3040/31 ms, matrix 384×384, TF 10, slice number 24), and spectral adiabatic inversion recovery T2-weighted sequence on the sagittal plane (FOV 250 mm, ST 3.0 mm, TR/TE 4,950/79 ms, matrix 384×384, TF 14, slice number 28). Intravenous injection of gadolinium (Magnevist®, Bayer HealthCare) was performed using an automatic injector at a standard dose of 0.1 mmol/kg (0.2 mL/kg) with a flow rate of 2.5 mL/s through a 20-G Abbocath® needle into a cubital vein. After injection, a modified T1-weighted fast 3D gradient-echo volumetric interpolated sequence (VIBE) with fat saturation was acquired (FOV 250 mm, ST 1.1 mm, section gap 0.22 mm, TR/TE 9.29/3.99 ms, matrix 256×256, flip angle 10°) in repeated acquisitions starting at 0:00, 0:28, 0:57, 1:26, 1:54, 2:23, 2:52, and 3:20 min post-contrast (scanning time, 28 s for each acquisition). They were then reconstructed in the coronal (slice number 43) and axial (slice number 48) planes at 0:00 min corresponding to the beginning of contrast injection. T1-weighted fast spin-echo sequences with fat saturation on the axial (FOV 230 mm, ST 3.5 mm, TR/TE 696/31 ms, matrix 384×384, TF 4, slice number 45) and coronal planes (FOV 250 mm, ST 2.0 mm, TR/TE 777/21 ms, matrix 384×384, TF 4, slice number 24) after contrast injection were also acquired.

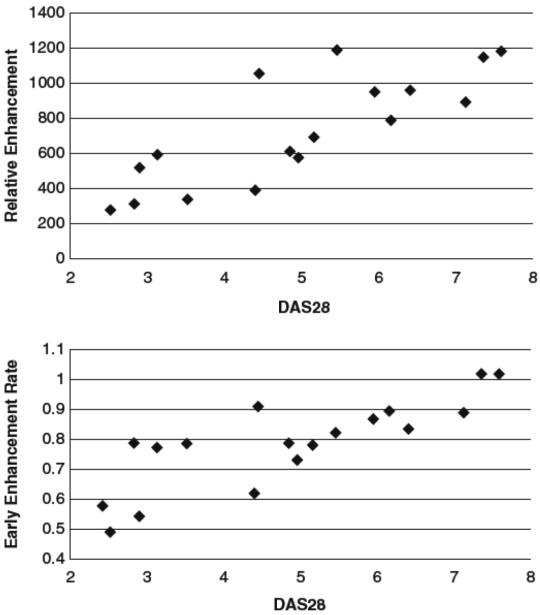



**Fig. 1** Representation of REDAS28 and EER-DAS28 values for individual patients. $p<0.0001$ for both correlations, Pearson's test

**Table 3** Comparison of the mean±SD values of RE, REE, and RAMRIS score for synovitis in patients with inactive (DAS28<3.2) and active (DAS28≥3.2) disease

| | DAS28<3.2 (*n*=5) | DAS28≥3.2 (*n*=13) | p[a] |
|---|---|---|---|
| RE | 312.0 (274) | 892.0 (508.2) | 0.0078 |
| REE | 0.5790 (0.2629) | 0.8354 (0.1185) | 0.0138 |
| RAMRIS synovitis[b] | 2 (4.5) | 8 (15) | 0.0432 |

Values are median (interquartile range)

[a] Mann-Whitney *U* test

[b] The value corresponds to the sum of the score obtained for each hand (calculated as described by Lassere et al. [32]) because both the hands were included in the FOV

MRI scoring was performed by an experienced musculoskeletal radiologist and included the quantification of synovitis at multiple places on the hands and wrist, according to the RA-MRI score (RAMRIS) defined by the OMERACT imaging studies [32], but with both hands included in the quantification.

The region of interest (ROI) for the dynamic study was selected on the basis of the unequivocal synovial tissue that showed a progressive enhancement on the reconstruction of the axial and coronal planes of the different dynamic acquisitions and the tissue that exhibited maximum visual enhancement. We used a small area (20–30 $mm^2$) while avoiding intra-articular fluid as identified by pre-contrast and dynamic sequences. Signal intensity/time curves were generated using the mean curve tools of Siemens Syngo® MR Workplace. The enhancement ratio of the synovial tissue was calculated in two ways: (1) as the rate of early enhancement (REE) during the first 55 s according to the formula $REE_{57}=S_{57}/S_{200}$, where $S_{57}$ and $S_{200}$ are the signal intensity 57 and 200 s after gadolinium injection, respectively and (2) as the relative enhancement (RE) according to the formula $RE=S_{200}-S_0$.

## Statistical analysis

Statistical analysis was performed using GraphPad InStat software (version 3.10). Categorical variables were expressed as proportions. Continuous variables were tested for normality with Kolmogorov-Smirnov test. Normal continuous variables were compared using Pearson's test correlation. Differences between two groups were assessed by the parametric *t*-test or the nonparametric Mann-Whitney *U*-test, according to their distribution. The diagnostic performance of MRI examination in terms of sensitivity and specificity was evaluated by Fisher's exact test. Specifically, the diagnostic accuracy was tested using an REE-predicted cutoff point of 0.778 for identifying patients with clinically active disease (DAS28≥3.2). Two-sided *p* values less than 0.05 were considered significant.

## Results

Sixteen women and two men with a median age of 46 years (range 16–67 years) were evaluated. The mean disease duration at the time of presentation was 6.2 months (range 2–11 months) with mean tender and swollen joint counts of 7.1 (range 1–17) and 4.8 (range 1–14), respectively. The mean ESR was 36.5 mm/h (range 2–120 mm/h), and the mean overall disease activity on a visual analog scale was quantified at 56.8 (range 10–94). The mean DAS28 score was 4.8 (range 2.42–7.59) (Table 1).

DCE-MRI was performed in all subjects without any discomfort or adverse effects.

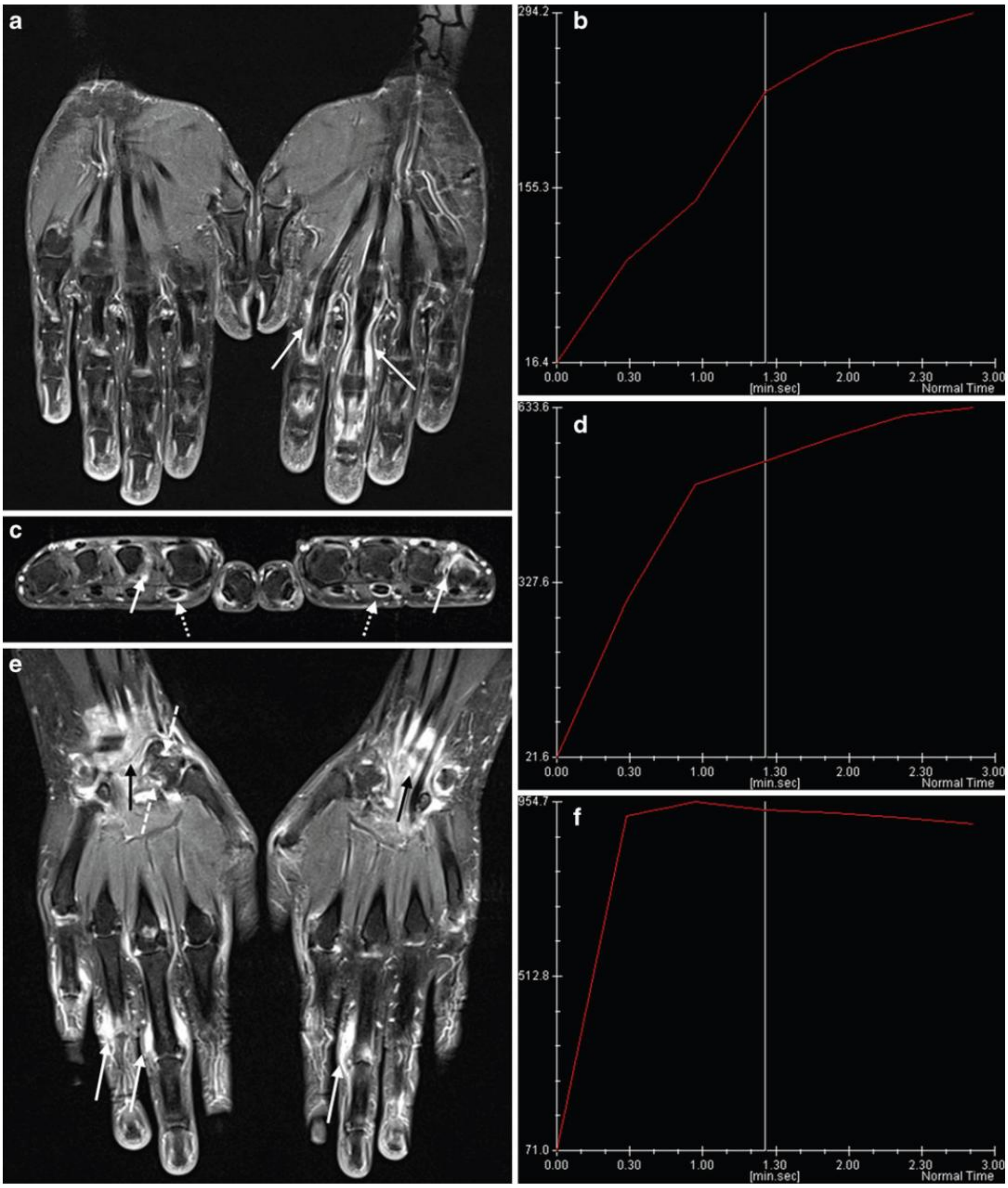
A significant correlation was observed between the parameters evaluated and DAS28 score; maximum correlation was observed between RE ($r=0.8331$, 95% CI=0.5993–0.9360, $p<0.0001$), REE ($r=0.8112$, 95% CI=0.5542–0.9270, $p<0.0001$), and RAMRIS score for synovitis ($r=0.7659$, 95% CI=0.4654–0.9081, $p<0.0002$) (Table 2); these findings are shown in Fig. 1.

Comparison between patients with inactive (DAS28<3.2) and active (DAS28≥3.2) disease revealed that median RE,

**Fig. 2 a, b** A 32-year-old man with early inflammatory arthritis, symptom duration of 3 months, and a DAS28 of 2.52 without criteria for a specific diagnosis at the time of examination. Coronal T1 fat-sat sequence after intravenous contrast administration, indicative of tenosynovitis (*arrows*) with a signal intensity/time curve after gadolinium representing a low EER pattern (EER 0.4915). **c, d** A 57-year-old woman with early inflammatory arthritis, symptom duration of 8 months, and a DAS28 of 4.85 who did not meet the criteria for a specific diagnosis at the time of examination, but met RA criteria at the 6-month clinical follow-up. Axial T1 fat-sat sequence after intravenous contrast administration, indicative of synovitis of the metacarpophalangeal joints (*arrows*) and tenosynovitis of the flexor tendons (*dashed arrows*) with a signal intensity/time curve after gadolinium representing an intermediate EER pattern (EER 0.7880). **e, f** A 56-year-old woman diagnosed with early RA, symptom duration of 5 months, and a DAS28 of 7.59. Coronal T1 fat-sat sequence after intravenous contrast administration, indicative of marked synovitis of the flexor tendons, radiocarpal and intercarpal joints (*black arrows*), proximal interphalangeal (*white arrows*), and trapezium erosions (*dashed arrows*) with a signal intensity/time curve after gadolinium representing a high EER pattern (EER 1.0184)

REE, and RAMRIS score for synovitis were greater in patients with active disease (892, 0.8354, and 8, respectively) than in patients with inactive disease (312, 0.5790, and 2, respectively); these differences were significant, most notably in cases of RE ($p$=0.0078) and REE ($p$=0.0138), but also with the RAMRIS score for synovitis ($p$=0.0432) (Table 3).

The test of the diagnostic accuracy of an REE-predicted cutoff point of 0.778 for identifying patients with clinically active disease (DAS28≥3.2) revealed a



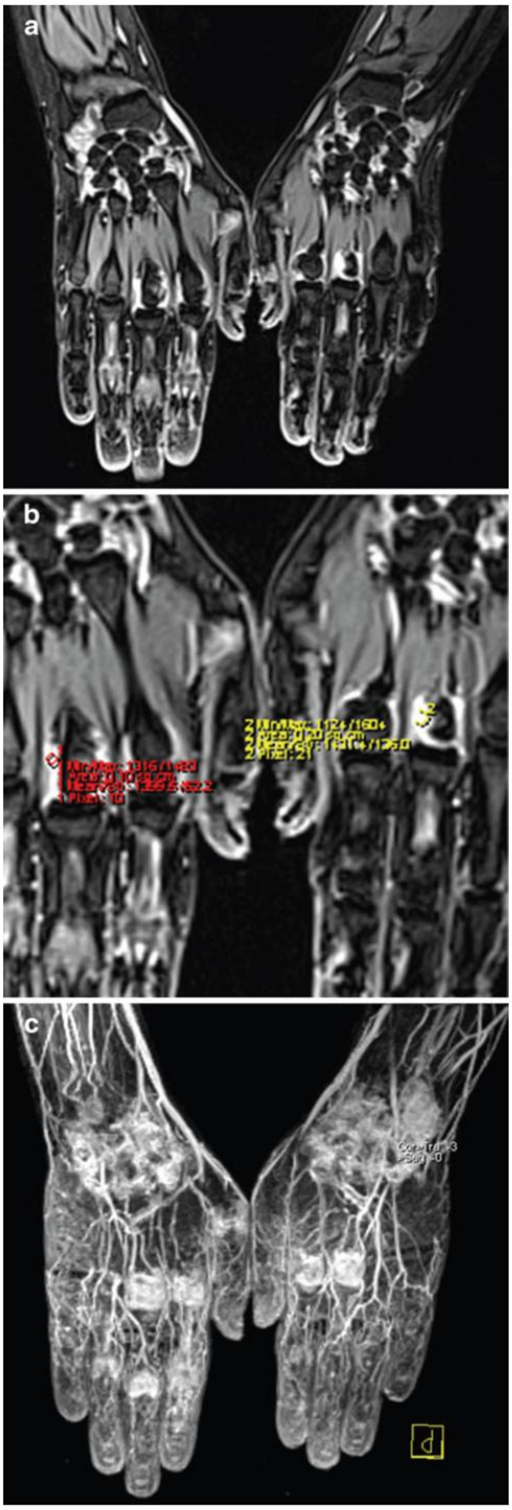



**Fig. 3** **a** A 43-year-old woman with early inflammatory arthritis, symptom duration of 2 months, and a DAS28 of 7.13 with the diagnosis of early RA at the time of examination. Coronal VIBE sequence with fat saturation after intravenous contrast administration, indicative of marked synovitis of the radiocarpal, intercarpal, and metacarpophalangeal joints. **b** Example of an ROI drawing. **c** Maximum intensity projection of a 3D digitally subtracted dataset of the third VIBE acquisition after contrast, indicative of increased vascularity of synovitis

sensitivity of 92% (95% CI 62–99%), specificity of 67% (95% CI 22–96%), positive predictive value of 85% (95% CI 55–98%), and a negative predictive value of 80% (95% CI 28–99%) ($p$=0.0217).

Figure 2 shows the typical MRI findings in patients with different levels of disease activity. Figure 3 gives an example of an ROI drawing on a coronal section obtained with the VIBE sequence.

## Discussion

The correlation between DCE-MRI parameters and clinical findings, including joint swelling [10], pain [10, 11], HAQ score [12], erosions [13], ESR [14], and treatment effects [15, 16], has previously been demonstrated. However, all these studies were performed using low-field MRI with somewhat complex formulae for enhancement quantification and involved patients with already established RA. The knee and wrist were most commonly assessed; however, in the latter case, only the dominant hand was evaluated [1, 7, 10, 11, 13–29]. This is a drawback if we consider the possibility of asymmetric disease. Our cohort included patients with early polyarthritis who were evaluated at high field strength; both hands were included in the FOV.

In this study, we evaluated rapidly acquired serial images within 3.48 min of administering intravenous gadolinium. We used a standardized infusion technique, as gadolinium diffusion and pharmacokinetics are influenced by these determinants, in an attempt to relate changes in the local diffusion of the contrast agent to the number, size, and permeability of the synovial vessels.

We used a dedicated protocol that strictly includes both hands in the FOV for a more precise quantification of the disease process; this enables accurate determination of RAMRIS score for both hands compared to the previous studies that included only the dominant hand [12, 18–21, 24, 25]. Including both hands in the FOV hinders the use of the dedicated hand and wrist coil. However, the image quality was not negatively affected because the surface coil performed extremely well owing to the greater field strength at 3-T with its high signal-to-noise and contrast-to-noise ratios [30], and the use of the VIBE sequence. This modified 3D fast gradient-echo sequence uses a symmetric echo in the read direction, partial in-plane Fourier sampling in the phase-encoding direction, and asymmetric echo sampling and sinc interpolation in the partition direction. It provides thinner sections, higher signal-to-noise ratio, higher image contrast, and shorter acquisition time than conventional sequences [35–37].

Despite the short acquisition time (28 s), the VIBE sequence obtained in this study has a higher temporal resolution than those obtained with some of the previously described dynamic protocols (acquisition times between 10 and 48 s). However, the lowest acquisition times in previous studies correspond to low spatial resolution, small FOV, or limited slice number [7, 15, 16, 21, 24]. We think that the nearly isotropic resolution of this sequence really compensates for the intermediate acquisition time for dynamic study. It allowed careful selection of an area of synovial tissue for dynamic study by drawing a small circular ROI precisely in the areas of progressive and late maximum enhancement on the images obtained from the different dynamic VIBE sequences. The most important factor to be considered was the unequivocal positioning of the ROI on the synovial tissue, avoiding intra-articular fluid (identified by the pre-contrast and dynamic sequences), vessels, or small parts other than synovitis. This was definitely best accomplished with small ROI and high-resolution images.

Our decision to use the dynamic parameters RE and REE as opposed to other possible measures such as maximum slope, maximum/static relative enhancement, or maximum enhancement rate was because of their simplicity and potential for routine clinical use. Moreover, for other parameters such as maximum slope higher temporal resolution protocol would be more appropriate; the acquisition times used in our study seem to be more adequate for RE and REE, which depend only on specific examination times.

We found that RE, REE, and RAMRIS score for synovitis were significantly correlated to DAS28 score, suggesting that these parameters, even in early disease, can reflect the actual degree of joint inflammation and disease activity. Some previous studies performed with established RA patients that mainly focused on rheumatoid knees found weak associations [9, 38] or no correlation between dynamic MRI and clinical and laboratory assessments [12, 39, 40]. We believe that our findings reflect the higher spatial resolution used and are a consequence of our decision to reconstruct on the axial and coronal planes for all the acquisitions of dynamic study, which enabled most precise selection of ROI location. The use of both hands for the RAMRIS quantification of synovitis as opposed to the previously validated technique using only the dominant hand was definitely responsible for the highly significant correlation between this parameter and DAS28 score. Using our method, even minor degrees of inflammation can be considered in both hands, allowing the calculation of a score that closely reflects disease activity with no additional cost or increase in examination time.

Cimmino et al. [12] previously presented significant differences between patients with active and inactive diseases with respect to parameters of synovial membrane enhancement on the wrist; however, they used a 0.2-T MRI unit. Ostergaard et al. [10] obtained similar findings but using the knee. In our study, we confirmed the discriminative ability of RE, REE, and RAMRIS score by using 3-T MRI and including both hands and wrists on the FOV.

In light of our finding of a precise correlation between DAS28 score and MRI parameters of disease activity at 3-T, we also aimed to identify a cutoff value for MRI measurements that can identify patients with active disease (DAS28≥3.2). To the best of our knowledge, this has never been reported by another group. We excluded RE from this evaluation because of the absence of a rate character for the parameter, which restricts its reproducibility with different equipment. In this respect, statistical analysis was limited by the small number of patients, hindering the receiver-operating curve analysis. Our best option was to select a predicted REE cutoff value of 0.778, which was adequate with a sensitivity of 92% and specificity of 67%. Nevertheless, a larger cohort in our prospective setting is necessary to verify these results.

The limitations of our study include its small sample size and the lack of a rate character for RE determination; this raises the already documented concerns regarding the reproducibility of dynamic MRI on different scanners [41].

Quantification of disease activity in early inflammatory arthritis by using 3-T DCE-MRI is easy to perform, lacks significant adverse effects, and can be frequently repeated. Prospective studies of pharmacological treatment and patient monitoring for responses to treatment on an individual basis can benefit from the precise and complete visualization of synovitis, bone marrow edema, and bone erosions that can be combined with functional information on disease activity.

In conclusion, our findings support the use of 3-T DCE-MRI for quantification of disease activity and for discriminating active disease from inactive disease in early polyarthritis. This technique could form an excellent strategy for initial characterization and long-term follow-up of patients.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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# PART II

## Bilateral Magnetic Resonance Imaging of the Hand and Wrist in Early and Very Early Inflammatory Arthritis: Tenosynovitis is Associated with Progression to Rheumatoid Arthritis

# Bilateral Magnetic Resonance Imaging of the Hand and Wrist in Early and Very Early Inflammatory Arthritis: Tenosynovitis is Associated with Progression to Rheumatoid Arthritis

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# Bilateral Magnetic Resonance Imaging of the Hand and Wrist in Early and Very Early Inflammatory Arthritis: Tenosynovitis is Associated with Progression to Rheumatoid Arthritis

**ORIGINAL RESEARCH**

**Advances in Knowledge**

1. Tenosynovitis is a major imaging finding in early rheumatoid arthritis (RA). Tenosynovitis of the extensor carpi ulnaris (odds ratio [OR], 3.21) and of the flexor tendons of the second finger (OR, 14.61) in the VERA group and synovitis of the radioulnar joint (OR, 8.79) and tenosynovitis of the flexor tendons of the second finger (OR, 9.60) in the ERA group were the most significantly associated with progression to RA ($p < 0.05$).

2. Inclusion of tenosynovitis as a scoring criterion might improve the diagnostic performance of the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) RA classification criteria. Consideration of tenosynovitis improved area under the curve values of the ACR/EULAR criteria performance for the diagnosis of RA from 0.942, $p < 0.0001$ (sensitivity, 52%; specificity, 100% for the cutoff score $\geq 6$) to 0.972, $p < 0.0001$ (sensitivity, 76%; specificity, 100% for the cutoff score $\geq 6$).

3. Magnetic Resonance Imaging (MRI) intimates that RA may start asymmetrically. Asymmetry was found in 80.0% and 69.3% of joint or tendon pairs of VERA and ERA patients, respectively ($p < 0.05$).

**Implication for Patient Care**

MRI can contribute for a better identification of RA patients with short duration of symptoms, the phase in which treatment makes the greatest difference.

**Summary Statement**

Tenosynovitis is a common imaging finding in early RA and its inclusion as a scoring criterion might contribute for a better diagnostic performance of the 2010 ACR/EULAR classification.

**Key words**:

Very early arthritis; early arthritis; rheumatoid arthritis; tenosynovitis; magnetic resonance imaging

**ABSTRACT**

**Purpose**

To identify bilateral hand and wrist findings of synovial inflammation that are associated with progression to Rheumatoid Arthritis (RA) in a very early arthritis cohort (VERA, disease duration < three months) and in an early arthritis cohort (ERA, disease duration < 12 months). Also to test tenosynovitis as an MRI additional parameter for improving the diagnostic accuracy of the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) RA classification criteria. Lastly, to evaluate the symmetry of joint and tendon involvement.

**Materials and Methods**

Institutional review board approval and informed patient consent were obtained. Thirty-five patients (32 women, 3 men; mean age 45 years) with untreated recent-onset inflammatory arthritis participated in this prospective study and were examined using an MRI approach including both wrists and hands. After a follow-up of 12 months, 25 patients fulfilled the criteria for RA (10 VERA patients and 15 ERA patients). Ten patients did not fulfil the criteria for RA (Non-RA) and had other diagnosis. Possible associations between synovitis for each joint and tendon and RA diagnosis at 12 months were tested by univariate logistic regression analysis. The diagnostic performance of the ACR/EULAR RA classification criteria was evaluated using receiver operating curve (ROC) analysis. Asymmetry prevalence was also calculated considering all the joints and tendons in the analysis.

**Results**

Tenosynovitis of the extensor carpi ulnaris (odds ratio [OR], 3.21) and of the flexor tendons of the second finger (OR, 14.61) in the VERA group and synovitis of the radioulnar joint (OR, 8.79) and tenosynovitis of the flexor tendons of the second finger (OR, 9.60) in the ERA group were the most significantly associated with progression to RA ($p < 0.05$). Consideration of tenosynovitis improved area under the curve values of the ACR/EULAR criteria performance for the diagnosis of RA from 0.942, $p < 0.0001$ (sensitivity, 52%; specificity, 100% for the cutoff score ≥ 6) to 0.972, $p < 0.0001$ (sensitivity, 76%; specificity, 100% for the cutoff score ≥ 6). Asymmetry was found in 80.0% and 69.3% of joint or tendon pairs of VERA and ERA patients, respectively ($p < 0.05$).

**Conclusion**

Tenosynovitis is an imaging finding in early RA, and its inclusion as a scoring criterion might contribute for a better diagnostic performance of the 2010 ACR/EULAR classification. Furthermore our study showed that early RA is an asymmetrical disease.

## INTRODUCTION

There is growing consensus that optimal management of rheumatoid arthritis (RA) requires both early diagnosis and aggressive early treatment.[1-3] However, therapeutic decisions are hindered by its non-specific early clinical features[4-7] thus the 1987 revised criteria for RA of the American College of Rheumatology (ACR; formerly the American Rheumatism Association)[8], have limited value for early arthritis.[9, 10] The new 2010 RA classification criteria of the ACR/European League against Rheumatism (ACR/EULAR)[11] described a new approach emphasising the identification of patients with relatively short duration of symptoms. However, the new criteria may still lead to significant over- and under-diagnosis within the first 3 months after symptom onset.[12] Therefore, the use of additional tests, namely more sensitive imaging techniques, would be helpful.

The synovium is targeted by the rheumatoid inflammatory process and synovial inflammation and thickening are the histologic hallmarks and the earliest abnormalities to appear in RA.[13] Magnetic resonance imaging (MRI) is already known as the non-invasive imaging modality of choice for visualisation of the inflamed synovium and is recognised as a useful tool for assessing established RA.[14] However, the value of MRI in diagnosing early RA has been less studied.[15-20] On the other hand high-field-strength magnetic resonance imaging at 3.0 Tesla (3-T MRI) is known to provide precise and complete morphological analysis of the hands and wrists[21] and the value of dynamic contrast-enhanced 3-T MRI for quantification of disease activity in early RA patients has been previously shown.[22] RA in the earlier stages is clinically characterised by a higher prevalence of asymmetry with a tendency towards symmetry as the disease progresses.[23-28] Despite this, previous early RA MRI studies have focused on only the dominant or else the clinically most affected hand. [13-20]

The tenosynovium produces proinflammatory cytokines and proteolytic enzymes in RA. Flexor tenosynovitis in the hands has already been identified as a frequent finding in early rheumatoid arthritis [29] as a risk factor for erosions [30, 31] and as a potential marker of response to biological treatment [32]. Despite this tenosynovitis of the wrists and hands has received far less attention in the literature than joint synovitis. One recent report identified flexor tenosynovitis diagnosed by MRI of the hand as a strong predictor of early rheumatoid arthritis.[33] However, the study included patients with disease duration up to

24 months, largely exceeding the currently accepted definitions of early RA (disease duration up to 12 months).[34, 35]

Therefore, we hypothesised that bilateral hands and wrist high field-strength MRI detection of tenosynovitis, combined with detection of joint synovitis, could have a discriminatory role in the identification of early arthritis patients with high probability of developing RA.

Thus our aim was to identify bilateral hand and wrist MRI findings of synovial inflammation in the tendons and joints that are associated with progression to RA in a very early arthritis cohort (patients who presented within 3 months of arthritis onset) and in an early arthritis cohort (patients who presented between 3 months and one year after arthritis onset).[36] Additionally, we aimed to test our tenosynovitis MRI findings as a new additional parameter for improving the accuracy of the 2010 ACR/EULAR RA classification criteria in early arthritis. It was also our purpose to evaluate symmetry of joint and tendon involvement

## MATERIALS AND METHODS

### Patients

From April 2009 until June 2011, thirty-five consecutive patients with untreated clinically apparent synovial swelling at four or more joints of a 68 joint count [37], including involvement of at least one joint of the wrists and hands (excluding the distal interphalangeal joints and the first carpometacarpal joint), and with a disease duration of less than 12 months were included in the study. The patients were recruited from the rheumatology outpatient clinics of Hospital da Luz and Hospital de Santa Maria, and the cohort included 32 women (median age of 46.5 years; range, 18–67 years) and 3 men (median age of 27.7 years; range, 19–32 years) with a global median age of 45 years (range, 18–67 years).

After a follow-up of 12 months, 25 patients fulfilled the criteria for RA according to the 1987 ACR criteria.[8] Of those, 10 patients had had a disease duration of less than three months at the time of MRI examination and were classified as very early RA (VERA), while 15 patients had had a disease duration of less than 12 months but more than three months and were classified as early RA (ERA) [36]. Ten patients with polyarthritis did not fulfil the criteria for RA and were classified as Non-RA (used as a control group).

Exclusion criteria included pregnancy (n = 0) or breast-feeding (n = 0); inability to give informed consent (n = 0); current use of glucocorticoids (n = 4), methotrexate (n = 2), or other disease-modifying anti-rheumatic drugs (n = 0); active malignancy (n = 1); cellulites (n = 0); osteomyelitis (n = 0); occupation or sports related overuse (n = 1); trauma (n = 0); and contraindications to performing an MRI (n = 2). All patients provided informed consent, and the study conformed to the ethical principles for medical research involving human subjects according to the World Medical Association Declaration of Helsinki. The study was approved by the local ethics committee.

### Clinical data

Demographic information including age and gender was collected. The type and distribution of initial joint symptoms, disease duration prior to presentation, number of tender and swollen joints of a 28-joint count,[35] and patient's overall disease activity on a visual analogue scale (VAS; range, 0–100 mm) were assessed (CR, 8 years experience Board certified Rheumatologist). The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, presence of immunoglobulin M (IgM) RF, and presence of anti-citrullinated protein antibodies (ACPA) were recorded. Disease activity was assessed by calculating the DAS28 score for each patient.[38] A diagnosis score for the time of initial presentation was calculated according to the 2010 RA classification criteria of the ACR/EULAR.[11]

**MRI imaging**

MRI examination of the wrists and hands was performed at 3.0-T (Magnetom Verio, Siemens Healthcare) using a six-channel surface phased-array body coil including both hands simultaneously in the field of view (FOV); the patient was placed in the prone position with the hands fixed side-by-side over the head with the help of several cushions. The following sequences were acquired before intravenous injection: T1-weighted fast spin-echo sequences on the axial (FOV, 230 mm; slice thickness (ST), 3.5 mm; repetition time (TR)/echo time (TE), 696/31 ms; matrix, 384 × 384; turbo factor (TF), 4; and slice number, 45) and coronal (FOV, 250 mm; ST, 2.0 mm; TR/TE, 583/21 ms; matrix, 384 × 384; TF, 4; and slice number, 24) planes, proton density-weighted fast spin-echo sequence with fat saturation on the coronal plane (FOV, 250 mm; ST, 2.0 mm; TR/TE, 3040/31 ms; matrix, 384 × 384; TF, 10; and slice number, 24), and spectral adiabatic inversion recovery T2-weighted sequence on the sagittal plane (FOV, 250 mm; ST, 3.0 mm; TR/TE, 4950/79 ms; matrix, 384 × 384; TF, 14; and slice number, 28). Intravenous injection of gadolinium (Magnevist®; Bayer HealthCare) at a standard dose of 0.1 mmol/kg (0.2 mL/kg) was performed using an automatic injector with a flow rate of 2.5 mL/s through a 20-G Abbocath® needle into a cubital vein. After injection, a modified T1-weighted fast 3D gradient-echo volumetric interpolated sequence with fat saturation was acquired (FOV, 250 mm; ST, 1.1 mm; section gap, 0.22 mm; TR/TE, 9.29/3.99 ms; matrix, 256 × 256; and flip angle, 10°) by repeated acquisitions starting at 0:00, 0:28, 0:57, 1:26, 1:54, 2:23, 2:52, and 3:20 min post-contrast administration (scanning time, 28 s for each acquisition); the acquisitions were then reconstructed in the coronal (slice number, 43) and axial (slice number, 48) planes at 0:00 min, corresponding to the beginning of contrast injection. T1-weighted fast spin-echo sequences with fat saturation on the axial (FOV, 230 mm; ST, 3.5 mm; TR/TE, 696/31 ms; matrix, 384 × 384; TF, 4; and slice number, 45) and coronal (FOV, 250 mm; ST, 2.0 mm; TR/TE, 777/21 ms; matrix, 384 × 384; TF, 4; and slice number, 24) planes were also acquired after contrast injection.

**MRI image evaluation**

MRI scoring was performed by two independent readers who were blinded to clinical data and by separate analysis of each set of images (MN, 4 years experience fellowship-trained musculoskeletal Board certified Radiologist, 9 years cross-sectional image interpretation experience; AG, 8 years experience fellowship-trained musculoskeletal Board certified Radiologist, 22 years cross-sectional image interpretation experience) and included the quantification of synovitis in multiple joints of the hands and wrists (distal radioulnar joint; radiocarpal joint; intercarpal and carpometacarpophalangeal, CMC, joints; metacarpophalangeal, MCP, joints; proximal interphalangeal, PIP, joints; excluding the $1^{st}$ CMC, the $1^{st}$ MCP and the $1^{st}$ PIP). A score of 0 to 3 was assigned for each joint, where 0 was normal with no synovial enhancement and 3 the maximum presumed volume of enhancing tissue in the synovial compartment, according to the RA-MRI score (RAMRIS) defined by Outcome Measures in Rheumatology (OMERACT) imaging studies.[39] Tenosynovitis scoring of post-contrast images on a 0 to 3 scale was performed as described by Haavardsholm et al.[40] but including six tendon groups on the dorsal side of the wrist (extensor pollicis brevis and abductor pollicis longus, extensor carpi radialis brevis and longus, extensor pollicis longus, extensor digitorum and indicis, extensor digiti minimi, and extensor carpi ulnaris) one tendon group on the ventral side of the wrist (flexor digitorium superficialis and profundus) and five tendon groups on the ventral side of the hand (first through fifth flexor tendons at the digit level). Both wrists and hands were included in the quantification. An aggregated synovitis score for each tendon or joint, obtained by adding the left and right scores, was used for the statistical analysis.

All the previously described joints or tendons were considered for symmetry evaluation. Pairs of joints or tendons were classified as asymmetrical when the absolute value of the difference in synovitis scores was one or more. Pairs of joints or tendons with no evidence of synovitis were excluded from the analysis, as they would artificially increase the symmetry prevalence.

**Statistical analysis**

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Baseline characteristics were described as proportions for categorical variables and median (interquartile range) values for continuous variables. All continuous variables were tested for normality with the Kolmogorov-Smirnov test. The Kruskal-Wallis test was used to identify differences between groups, and the Mann-Whitney test was used for the post-hoc paired comparisons.

Possible associations between synovitis for each joint and tendon and for each group of joints and tendons and RA diagnosis at 12 months were tested by univariate logistic regression, considering in the analysis the variables with statistically significant differences in the post-hoc paired comparisons. The goodness of the fit of the model was evaluated by Hosmer & Lemeshow test and the accuracy of the predictive model was tested using c statistic.

The diagnostic performance of the ACR/EULAR RA classification criteria [11] was evaluated using receiver operating curve (ROC) analysis. The diagnostic accuracy was tested again after adding score points to patients with tenosynovitis as identified by MRI with consideration for the tendons with statistically significant involvement in the inter-group comparison. Z statistic was used for pairwise comparison of ROC curves.

The difference between the proportions of asymmetry in different groups was tested by the chi-square test.

The inter-reader reliability was assessed using unweighted Cohen's kappa (k) statistics. Values of k <0.20 were considered to reflect poor agreement, 0.21 - 0.40: fair, 0.41 - 0.60: moderate, 0.61 – 0.80: good, >0.81: excellent.

## RESULTS

### Cohort characteristics

The demographic and clinical characteristics of the 35 patients at baseline are shown in Table 1 and are divided into groups according to their diagnoses at the 12-month follow-up. The Non-RA group included one patient with systemic lupus erythematosus and 9 with undifferentiated arthritis (5 cases of which were self-limited).

### Comparison of the median values of the synovitis scores for each of the joints and tendons and association between baseline MRI findings and 12-month RA diagnosis

A comparison of the median values of the synovitis scores for each joint and tendon investigated between VERA or ERA patients and Non-RA patients is presented in Table 2. Associations between baseline joint or tendon synovitis and RA diagnosis at 12 months were tested. Synovitis of the radiocarpal joint, flexor tendons of the second finger at the digit level, and extensor carpi ulnaris for VERA patients and of the flexor tendons of the second finger at the digit level, radioulnar and radiocarpal joints for ERA patients were significantly associated with RA diagnosis ($p < 0.05$) (Table 2; Figure 1, 2).

### Comparison of the median synovitis scores by joint and tendon groups and the association between baseline MRI findings and 12-month RA diagnosis

A comparison of the median values of the synovitis scores by groups of joints and tendons between VERA or ERA patients and Non-RA patients is presented in Table 3.

Associations between baseline synovitis by joint and tendon groups and RA diagnosis at 12 months were tested. Synovitis of the flexor tendons for VERA patients and of the radiocarpal and metacarpophalangeal joints for ERA patients was significantly associated with RA diagnosis ($p < 0.05$).

### Symmetry evaluation

Evaluation of MRI images revealed that if pairs of joints or tendons were classified as asymmetrical when the absolute value of the difference in synovitis scores was one or more, asymmetry was found in 80.0% of VERA, 69.3% of ERA, and 69.6% of Non-RA patients. The differences between the different groups were statistically significant ($p < 0.05$) with the exception of ERA versus Non-RA group comparison.

### Performance of the 2010 ACR/EULAR criteria in identifying RA patients

For the purpose of ROC analysis, VERA and ERA patients were considered as one group (RA). Evaluation of the performance of the 2010 ACR/EULAR criteria for identifying RA patients revealed that the use of the criteria as previously described[9] for identifying RA resulted in a sensitivity of 52% and specificity of 100% with an area under curve (AUC) of 0.942. Adding one score point to each patient with at least one of the most significant tendons (as identified in Table 2) affected by synovitis resulted in a sensitivity of 76%, specificity of 100% and an AUC of 0.972. Adding an additional score point to each patient with at least 3 of those tendons affected by synovitis resulted in a sensitivity of 80%, specificity of 100% and an AUC of 0.976. No significant differences were identified in pairwise comparison of ROC curves. (Table 4; Figure 3).

### Reliability

The inter-reader agreement was good for both tenosynovitis and synovitis scores (k=0.782 and k=0.798, respectively).

**DISCUSSION**

Our study identified tenosynovitis as a discriminating factor of the evolution towards RA in patients with arthritis for less than 3 months' duration (VERA). Tenosynovitis of the extensor carpi ulnaris and of the flexor tendons of the second finger were recognised as significantly associated with progression to RA in this cohort in addition to radiocarpal joint synovitis. Even in patients with longer disease duration (3–12 months), tenosynovitis of the flexor tendons of the second finger remained one of the significant discriminating features for fulfilling RA criteria. Another result of this study is the demonstration that including MRI-identified tenosynovitis in the 2010 ACR/EULAR classification criteria for RA improves score performance.

In view of our results, it seems peculiar that tenosynovitis of the wrists and hands has received so little attention in previous literature. In fact, there is no OMERACT RA-MRI[39] definition of the term 'tenosynovitis' and despite the proposal of an MRI tenosynovitis score for established disease[40], its use has been sparse. Even the report by Chand et al.,[41] the only available study applying 3-T MRI to the study of early RA patients, focused only on joint synovitis by describing a method for determining the synovial membrane volume.

The study by Eshed et al.[33] identified flexor tenosynovitis of the hand as a strong predictor of early RA. However, this work was performed with a low-field-strength extremity MRI unit (0.2 T).] There are other limitations in that study, such as the inclusion of patients with disease durations up to 24 months, which exceeds the currently accepted definitions of early RA,[34, 35] and the focus on groups of tendons, masking potential findings for individual tendons. An interesting recent study of synovitis maps by Karlo et al. [42] included tenosynovitis evaluation but it addressed unspecified inflammatory disorders. The other reports on the study of tendons by MRI in the context of RA are out of the scope of our current study because they have either focused on predicting tendon rupture in early RA [43] or assessed established long standing disease.[44-46]

In our bilateral study, making use of 3-T MRI technique, joint asymmetry rates of three quarters in VERA patients and two thirds in ERA patients were detected. This is in line with previous clinical descriptions of early RA depicting asymmetric joint involvement in 30–94% of patients and symmetrisation with RA progression.[23-28, 47] Taken together, these findings provide a morphological confirmation that early RA may be an asymmetrical disease.

Inter-group analysis revealed that in the VERA group compared to the Non-RA group, the most significant differences were found for the flexor and extensor tendons. Regression analysis identified flexor tendons as the best discriminating factor between VERA and Non-RA patients. Involvement of the flexor tendons in the ERA group remained significantly different from that in the Non-RA group, but the metacarpophalangeal and carpal joints had also highly significant synovitis involvement.

We tried to identify a strategy by which tenosynovitis could contribute to improvement of the diagnostic performance of the 2010 ACR/EULAR RA classification criteria.[11] The mean ACR/EULAR score in our VERA and ERA cohort was less than 6, confirming that some patients were not being identified as having RA at the time of presentation by the new criteria. Our results agree with those of a recent study with a very early inflammatory arthritis cohort that highlighted that despite improved performance of the 2010 criteria, over- and under-diagnosis may still remain important issues.[12, 48] In fact, in our cohort of RA patients, the ACR/EULAR criteria diagnostic performance in terms of AUC was improved by the addition of one score point to each patient with at least one of the most significant tendons affected by synovitis. Although representing a clear tendency the difference was not statistically significant. We believe that small sample size was a main limitation to z statistics performance; these findings need to be explored on larger numbers. Adding 2 score points to each patient with at least 3 of those tendons affected by synovitis did not further improve diagnostic performance. Joint synovitis was not considered in this analysis, as joint involvement that is clinically identified and/or confirmed by imaging studies, is already a parameter of the original 2010 ACR/EULAR criteria.

One of the limitations of our study was its small sample size which prevented multivariate regression analysis. Small sample size was related to the strict inclusion criteria, namely disease duration and the prospective nature of the study. However, we believe that the homogeneity of the groups in the study could mitigate this fact. Degeneration, impingement and overuse are known causes of tenosynovitis [49] and could also be a source of bias. Still, we believe that the recruitment from the rheumatology outpatient clinics of patients with clinical involvement of four or more joints, the exclusion of typical degenerative territories from the joint count (distal interphalangeal joints and the first carpometacarpal joint) [49] and the exclusion of patients with obvious occupation or sports related symptoms should lessen this problem.

Although tendinosis) may cause MRI signal changes within tendons, studies have shown the established pathology to consist of tendon degeneration with a complete absence of inflammatory cells.[50-52 In contrast, in RA the synovium is directly targeted by the rheumatoid inflammatory process and synovial thickening is the histologic hallmark and the earliest abnormality [13]. In this way, evaluation of tendinosis or other intrasubstance tendon characteristics was out of the scope of this study that focused on synovial membrane evaluation.

In conclusion, our data confirm that tenosynovitis is a common imaging finding in early RA and its inclusion as a scoring criterion might contribute for a better diagnostic performance of the 2010 ACR/EULAR classification. In addition, our study identifies early RA as an asymmetrical disease, suggesting the importance of a bilateral acquisition protocol.

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**Table 1.** Demographic, clinical, and laboratory data of patients at baseline

| Characteristic | VERA (n = 10) | ERA (n = 15) | Non-RA (n = 10) |
|---|---|---|---|
| Number (men/women) | 0/10 | 0/15 | 3/7 |
| Age (y) | 50.5 (20.25) | 48.0 (21.0) | 33.0 (15.5) |
| Disease duration (mo) | 2.5 (1) | 9.0 (3.5) | 9.5 (5.0) |
| Tender joint count[a] | 7.5*# (4.25) | 8.0*# (8.5) | 3.5*# (3.0) |
| Swollen joint count[a] | 3.0*# ± (1.75) | 4.0*# (6.0) | 2.0*# (2.5) |
| ESR (mm/h) | 22.5*# (22) | 33.0*# (33.5) | 6.5*# (5.5) |
| Overall disease activity (VAS) | 55 (28.75) | 75 (38) | 57.0 (28.25) |
| DAS28 | 5.17*# ± (0.95) | 4.85*# (1.19) | 3.5*# (1.11) |
| ACR/EULAR | 5*# ± (2) | 6.0*# (2.0) | 3.0*# (1.5) |

Except where indicated, the values are median (interquartile range, IQR)

Kruskal-Wallis test; * represents $p < 0.05$

Post hoc analysis using Mann-Whitney U test for VERA vs Non-RA and ERA vs Non-RA group comparison; # represents $p < 0.05$

[a]from 28-joint count

ACR/EULAR, score for RA according to the 2010 American College of Rheumatology/European League against Rheumatism classification criteria; DAS28, 28-joint disease activity score; ERA, early rheumatoid arthritis; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; VAS, visual analogue scale; VERA, very early rheumatoid arthritis

**Table 2.** Comparison of the median (IQR) values of synovitis scores for VERA and ERA patients and the association between baseline MRI findings and 12-month RA diagnosis (univariate logistic regression): Individual joint and tendon analysis

| MRI Synovitis | VERA (n = 10) | ERA (n = 15) | Non-RA (n = 10) | VERA | | | ERA | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | OR (95%CI) | $R^2$ (HL) | p (cstat) | OR (95%CI) | $R^2$ (HL) | p (cstat) |
| MCP3 | 0 (1.25) | 1# (3.00) | 0# (0.00) | | | | 1.66 | 0.44 | 0.99 |
| RadUln | 0 (1.25) | 3# (3.00) | 0# (0.00) | | | | 8.79 (1.02-75.63) | 0.47 (0.18; 0.98) | **0.04** (0.883) |
| RadCarp | 3# (2.25) | 2# (4.00) | 0# (1.25) | 3.00 (1.19-7.58) | 0.29 (5.26; 0.15) | **0.02** (0.800) | 2.21 (1.03-4.78) | 0.21 (3.44; 0.33) | **0.04** (0.747) |
| CMC | 0 (1.25) | 1# (4.00) | 0# (0.00) | | | | 3.59 | 0.27 | 0.12 |
| PIP4 | 0 (1.00) | 2# (3.00) | 0# (1.25) | | | | 2.03 | 0.18 | 0.06 |
| Ext Comp6 | 2# (4.25) | 0# (3.00) | 0 (0.00) | 3.21 (1.09-9.40) | 0.39 (0.43; 0.81) | **0.03** (0.825) | 2.15 | 0.14 | 0.16 |
| Flex Wrist | 0# (2.50) | 0# (2.00) | 0# (0.00) | 1.09 | 0.28 | 0.99 | 1.75 | 0.30 | 0.99 |
| Flex Dig2 | 1.5# (3.25) | 1# (3.00) | 0# (0.00) | 14.61 (1.09-194.6) | 0.48 (0.05; 0.99) | **0.04** (0.875) | 9.60 (1.17-78.93) | 0.39 (0.09; 0.96) | **0.03** (0.840) |
| Flex Dig3 | 2# (3.00) | 1# (2.00) | 0# (0.00) | 4.43 | 0.35 | 0.10 | 7.66 | 0.24 | 0.06 |

For table simplicity only the results for joints or tendons with differences between groups are presented, as identified by $p < 0.05$ in Kruskal-Wallis test.

Post hoc analysis using Mann-Whitney U test for VERA vs Non-RA and ERA vs Non-RA group comparison; # represents $p < 0.05$.

Univariate logistic regression; OR, odds ratio; 95% CI, 95% confidence interval; cstat, c statistic; HL, Hosmer & Lemeshow test for goodness of fit (chi-squared; p-value); R2, Cox & Snell R square; p values given in bold are significant.

CMC, intercarpal-carpometacarpal joint; ERA, early rheumatoid arthritis; Ext Comp6, sixth extensor tendon compartment (extensor carpi ulnaris); Flex Wrist, flexor tendons at the wrist level; Flex Dig2, flexor tendons of the second finger at the digit level; Flex Dig3, flexor tendons of the third finger at the digit level; IQR, interquartile range; MCP3, metacarpophalangeal joint of the third finger; PIP4, proximal interphalangeal joint of the fourth finger; RA, rheumatoid arthritis; RadCarp, radiocarpal joint; RadUln, radioulnar joint; VERA, very early rheumatoid arthritis.

Results are from the observer MN.

**Table 3.** Comparison of the median (IQR) values of synovitis scores for VERA and ERA patients and the association between baseline MRI findings and 12-month RA diagnosis (univariate logistic regression): Joint and tendon analysis by group

| MRI Synovitis | VERA (n = 10) | ERA (n = 15) | Non-RA (n = 10) | VERA | | | ERA | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | OR (95%CI) | $R^2$ (HL) | p (cstat) | OR (95%CI) | $R^2$ (HL) | p (cstat) |
| MCP2–5 | 1* (4.25) | 4*# (6.00) | 0*# (0.25) | | | | 3.65 (1.15-11.60) | 0.49 (0.33; 0.99) | **0.03** (0.903) |
| Carpal | 3.5*# (5.25) | 5*# (9.00) | 0*# (0.20) | 1.98 | 0.27 | 0.06 | 2.32 (1.06-5.09) | 0.43 (2.35; 0.79) | **0.04** (0.887) |
| PIP2–5 | 3 (2.5) | 4 (10.00) | 2.5 (4.25) | | | | | | |
| Extensor | 2*# (5.75) | 1*# (6.00) | 0*# (0.00) | 3.09 | 0.38 | 0.07 | 2.64 | 0.25 | 0.10 |
| Flexor | 5.5*# (5.5) | 5*# (8.00) | 0*# (0.00) | 4.28 (0.98-18.61) | 0.54 (0.19; 0.98) | **0.04** (0.930) | 2.63 | 0.39 | 0.08 |

Kruskal-Wallis test; * represents $p < 0.05$.

Post hoc analysis using Mann-Whitney U test for VERA vs Non-RA and ERA vs Non-RA group comparison; # represents $p < 0.05$.

Univariate logistic regression; OR, odds ratio; 95% CI, 95% confidence interval; cstat, c statistic; HL, Hosmer & Lemeshow test for goodness of fit (chi-squared; p-value); R2, Cox & Snell R square; p values given in bold are significant.

Carpal, carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints; ERA, early rheumatoid arthritis; Extensor, six extensor tendon groups on the dorsal side of the wrist, as described in the Methods section; Flexor, six tendon groups on the ventral side of the wrist and hand, as described in the Methods section; MCP2–5, second through fifth metacarpophalangeal joints; MRI, magnetic resonance imaging; PIP2–5, second through fifth interphalangeal joints; RA, rheumatoid arthritis; VERA, very early rheumatoid arthritis.

Results are from the observer MN

**Table 4.** Performance of the ACR/EULAR criteria for identifying RA patients and the role of tenosynovitis as detected by MRI

| Criteria | Sensitivity | Specificity | AUC | 95% CI | p* |
|---|---|---|---|---|---|
| ACR/EULAR ≥ 6 | 52 | 100 | 0.942 | 0.802-0.991 | **<0.0001** |
| ACR/EULAR+1 ≥ 6 | 76 | 100 | 0.972 | 0.852-0.999 | **<0.0001** |
| ACR/EULAR+2 ≥ 6 | 80 | 100 | 0.976 | 0.858-1.000 | **<0.0001** |

*ROC analysis.

Sensitivity, specificity values are given as percentages.

ACR/EULAR ≥ 6, performance of ACR/EULAR score greater than or equal to six for identifying RA patients; ACR/EULAR+1 ≥ 6, performance of ACR/EULAR score ≥6 for identifying RA patients, adding one score point to each patient with at least one of the tendons with statistically significant involvement in the inter-group comparison (as identified in Table 2) affected by synovitis; ACR/EULAR+2 ≥ 6, performance of ACR/EULAR score ≥6 for identifying RA patients, adding an additional score point to each patient with at least 3 of the tendons with statistically significant involvement in the inter-group comparison (as identified in Table 2) affected by synovitis.

ACR/EULAR, American College of Rheumatology/European League against Rheumatism; AUC, area under the receiver operating characteristic curve; MRI, magnetic resonance imaging;.

**FIGURE LEGENDS**

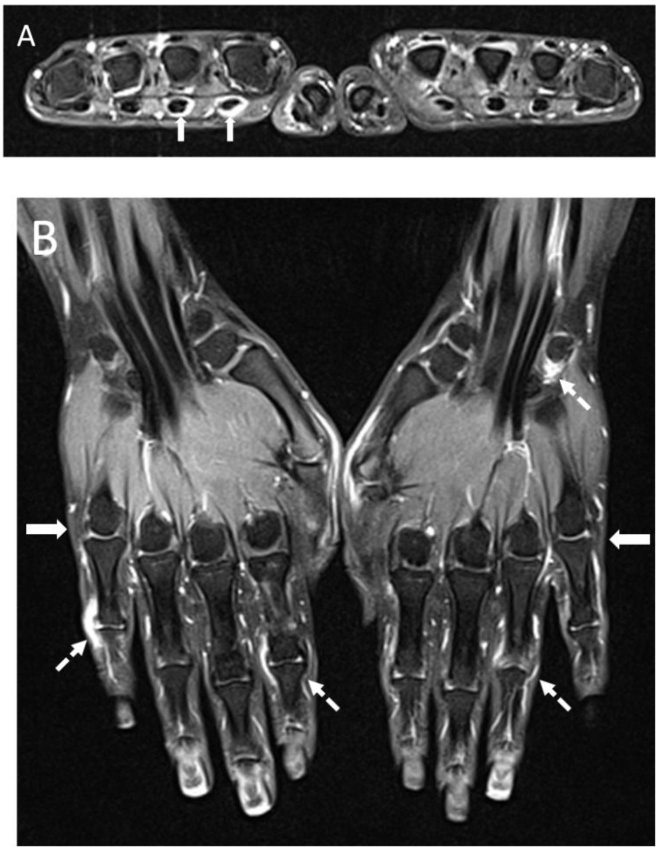


**Figure 1** Bilateral magnetic resonance imaging (MRI) of the hand and wrist of a 33-year-old woman with early inflammatory arthritis with a disease duration of 3 months; she did not fulfil the criteria for a specific diagnosis at the time of MRI examination (with a calculated score at presentation of 5 according to the 2010 rheumatoid arthritis (RA) classification criteria of the American College of Rheumatology/European League against Rheumatism), but did fulfil both the 1987 ACR and 2010 RA classification criteria for RA at the 12-month clinical follow-up. (A) Axial T1 fat-sat sequence after intravenous contrast administration showing grade 2 (≥2 and <5 mm synovial proliferation with enhancement) tenosynovitis of the flexor tendons of the second and third digits on the right (arrows). (B) Coronal T1 fat-sat sequence after intravenous contrast administration at the metacarpophalangeal joint level (arrows), demonstrating absence of metacarpophalangeal joint synovitis. Bilateral interphalangeal joint synovitis and left radiocarpal joint synovitis (pisotriquetral synovial recess) is noted (dashed arrows).

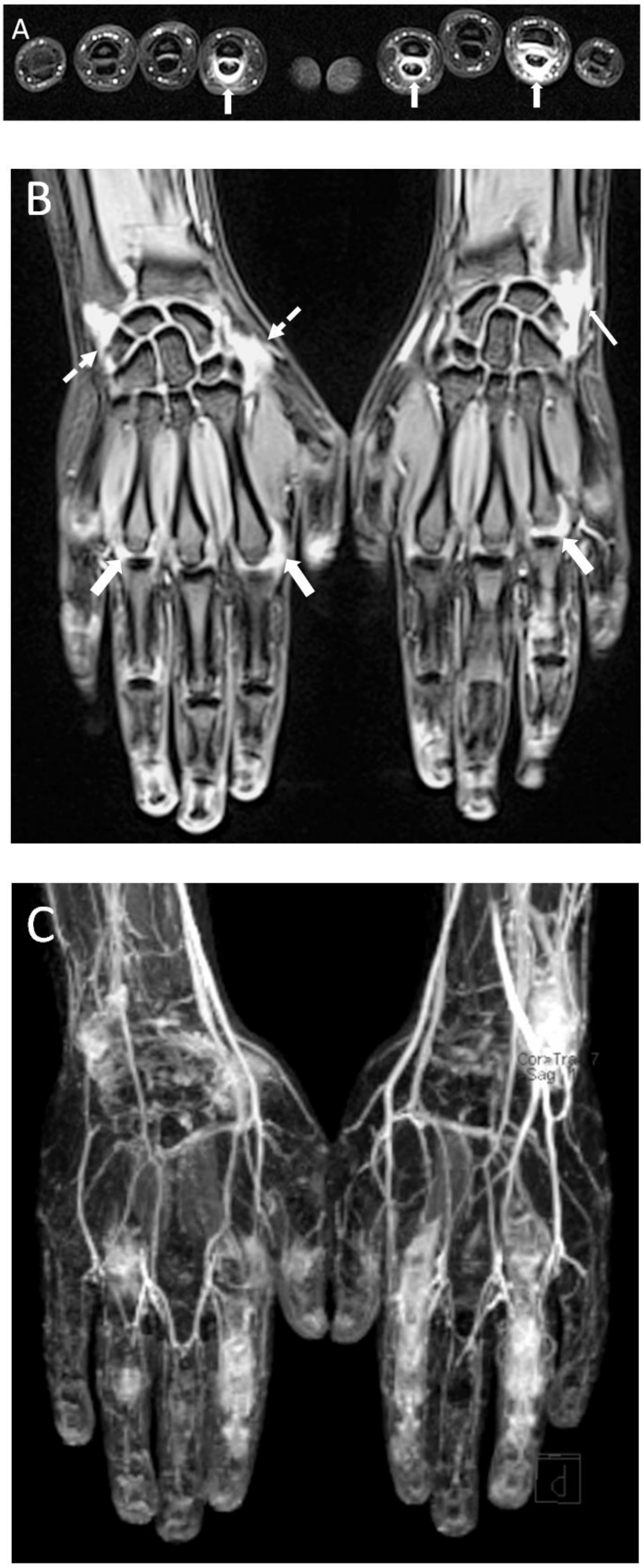


**Figure 2** Bilateral magnetic resonance imaging of the hand and wrist of an 18-year-old woman with early inflammatory arthritis with a disease duration of 8 months; she fulfilled the criteria for rheumatoid arthritis

at presentation. (A) Axial T1 fat-sat sequence after intravenous contrast administration showing tenosynovitis of the flexor tendons of the second and fourth digits on the left and of the second digit on the right (arrows). (B) Coronal high-resolution volumetric interpolated breath-hold (VIBE) sequence with fat saturation (slice thickness, 1.1 mm) after intravenous contrast administration, indicative of synovitis of the second and fourth metacarpophalangeal joints on the right and of the fourth metacarpophalangeal joint on the left (arrows), as well as of the left extensor carpi ulnaris (thin arrow) and the radiocarpal and trapeziometacarpal joints (dashed arrows). (C) Maximum intensity projection of a 3D digitally subtracted dataset of the VIBE acquisition after contrast administration, demonstrating increased vascularity of synovitis and tenosynovitis. The tube-like appearance of digit tenosynovitis is clearly depicted.

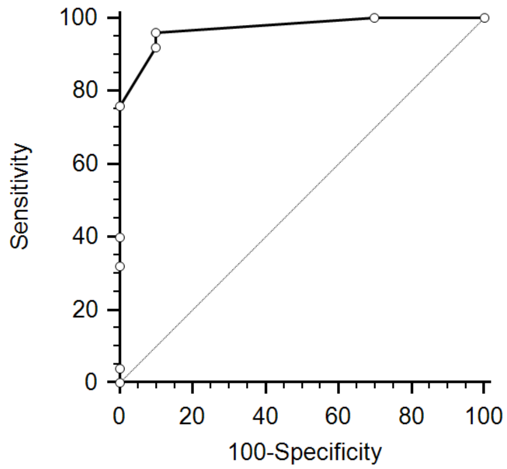


**Figure 3** ROC curve for RA as an outcome using ACR/EULAR score ≥6 for identifying RA patients, adding one score point to each patient with at least one of the tendons with statistically significant involvement in the inter-group comparison (as identified in Table 2) affected by synovitis (AUC, 0.972; 95% CI, 0.852-0.999). Sensitivity, specificity and criterion values for the nine operating points in the curve in order of increasing sensitivity: 1.2, 100, >8.70; 5.7, 100, >7.94; 32.9, 100, >6.88; 41.0, 100, >5.97; 78.1, 98.7, >4.87; 93.4, 90.0, >3.65; 96.0, 90.0, >3; 100.0, 29.0, >1; 100.0, 1.8, >1.

# PART III

## Bilateral Evaluation of the Hand and Wrist in Untreated Early Inflammatory Arthritis: a Comparative study of Ultrasonography and Magnetic Resonance Imaging

# Bilateral Evaluation of the Hand and Wrist in Untreated Early Inflammatory Arthritis: a Comparative study of Ultrasonography and Magnetic Resonance Imaging

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**ABSTRACT**

**Purpose**

To compare Doppler Ultrasound (US) and magnetic resonance imaging at 3.0 Tesla (3.0-T MRI) findings of synovial inflammation in the tendons and joints in an early polyarthritis cohort (patients who presented less than one year after arthritis onset) using a bilateral hand and wrist evaluation. To evaluate the diagnostic performance of US and MRI findings for RA, their ability to predict RA as a diagnostic outcome and their capacity to improve the accuracy of the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) RA classification criteria in early arthritis

**Methods**

Forty-five patients (40 women, 5 men; mean age 45.6 years) with untreated recent-onset polyarthritis participated in this prospective study and were examined using an US and MRI approach including both wrists and hands.

After a follow-up of 12 months, patients were classified as having RA if they fulfilled the criteria for RA (ERA patients).The proportion of synovitis identified by US and MRI for each joint and tendon region was compared by the qui-square test. The diagnostic performance of US and MRI for RA identification was evaluated using receiver operating curve (ROC) analysis. Possible associations between synovitis for each joint and tendon region as identified by US or MRI and RA diagnosis at 12 months were tested by logistic regression analysis. The diagnostic performance of the ACR/EULAR RA classification criteria corrected by US and MRI joint and tendon counts was evaluated using ROC analysis.

**Results**

30 patients fulfilled the ACR/EULAR criteria (ERA patients) and the remaining 15 failed to meet these criteria (non RA).

Carpal joints synovitis and tenosynovitis of the flexor tendons was found in 86.7% and 86.7% of ERA patients on MRI compared with 63.3% and 50% on US, respectively ($p < 0.05$). The global MRI and US counts revealed a good diagnostic performance for RA diagnosis of both techniques although statistically significantly higher for MRI (AUC = 0.959 and AUC = 0.853, respectively; z statistic = 2.210, $p < 0.05$).

MRI identification of carpal joint synovitis (OR = 3.64; 95% CI, 1.119 – 11.841) tenosynovitis of the flexor tendons (OR = 5.09; 95% CI, 1.620 – 16.051) and global joint and tendon count (OR = 2.77; 95% CI, 1.249 – 6.139) were in the multivariate logistic regression model the most powerful predictors of evolution towards RA. In the group of ERA patients with US joint and tendon counts ≤ 10 a statistically significant difference was found between the diagnostic performance for RA of the ACR/EULAR criteria as previously described and the diagnostic performance of the MRI corrected ACR/EULAR criteria (AUC = 0.898 and AUC = 0.986, respectively; z statistic = 2.181, $p < 0.05$).

**Conclusions**

3-T MRI identifies a higher prevalence of synovitis in comparison to US in an early polyarthritis cohort. Both techniques have a good diagnostic performance for RA although MRI reveals a significantly higher diagnostic capability. Synovitis of the carpal joints and of the flexor tendons as identified by MRI were the most powerful predictors of evolution towards RA. In patients with US joint and tendon counts ≤ 10, MRI can significantly improve the diagnostic performance of the 2010 ACR/EULAR classification criteria.

**Key words**: Early arthritis; rheumatoid arthritis; magnetic resonance imaging; ultrasound; ACR/EULAR

## INTRODUCTION

Early and aggressive use of disease-modifying drugs in rheumatoid arthritis (RA) is a crucial aspect of RA management [1-5]. However, therapeutic decisions are still hindered by non-specific early clinical and laboratorial features of RA [6-9]. The new 2010 RA classification criteria issued by the American College of Rheumatology / European League against Rheumatism (ACR/EULAR)[10] tried to highlight the need for the identification of very early arthritis patients at high risk for progressing into RA [11] and thus needing early aggressive treatment, thus avoiding the conservative approach of the 1987 ACR revised criteria for RA (ACR; formerly the American Rheumatism Association)[12], who were very specific for established arthritis but had a low sensitivity for detecting early RA.[13,14]. In fact, the new criteria may still lead to significant over- and under-diagnosis within the first months after symptoms onset[15] and may miss patients with symmetrical seronegative arthritis and limited joint involvement [16]. Therefore, the identification of additional more sensitive and specific tests for the very early detection of RA is a relevant unmet need in the field of Rheumatology.

Synovial thickening is the histologic hallmark and the earliest abnormality to appear in RA.[17] The role of ultrasound (US) and of magnetic resonance imaging (MRI) in identifying synovial thickening, optimizing diagnosis, measuring disease activity and identifying prognostic factors in RA has been largely studied [17, 18].

Ultrasound is already known to have a better reliability in comparison to clinical indices for synovitis evaluation [19] and there is accumulating evidence of its usefulness for the diagnosis and monitoring of several rheumatic disorders [20]. However, US can be time consuming, has a long learning curve and is operator dependent [20, 21]. Magnetic resonance imaging provide a better morphologic characterization than US and is generally recognized as the non-invasive imaging modality of choice for visualisation of the inflamed synovium in established RA and is increasingly being used in the assessment of early RA [17]. Nonetheless, MRI pose financial constraints, requires a larger period of time for the examination than US and sometimes needs the administration of an EV contrast agent [21]. In this way the comparative evaluation of the diagnostic performance and determination of the added value of each technique could have a critical role in patient management.

Studies comparing the diagnostic performance of US with MRI in early arthritis have been focused only on the dominant or the clinically most affected hand, with alternative study of joint or tendon disease and have used a low magnetic field (less than 1.5 Tesla) [22, 23 24]. These limitations may have hindered an adequate comparison of the performance of US and MRI in early RA.

To the best of our knowledge, there is no reported comparison between Doppler US and 3-T MRI findings in early RA.

Our aim was to compare Doppler US and high field strength 3-T MRI findings of synovial inflammation in the tendons and joints in an early polyarthritis cohort (patients who presented less than one year after polyarthritis onset) using a bilateral hand and wrist evaluation. Additionally, we aimed to evaluate the diagnostic performance of US and MRI findings and their ability to predict evolution into RA. It was also our purpose to compare US and MRI joint and tendon count in their ability to improve the accuracy of the 2010 ACR/EULAR RA classification criteria in early arthritis.

## MATERIALS AND METHODS

### Patients

From April 2009 until February 2012, forty-five consecutive patients with untreated clinically apparent synovial swelling at four or more joints of a 68 joint count [25], including involvement of at least one joint of the wrists and hands (excluding the distal interphalangeal joints and the first carpometacarpal joint), and with a disease duration of less than 12 months were included in the study. The patients were recruited from the rheumatology outpatient clinics of Hospital da Luz and Hospital de Santa Maria in Lisbon, and the cohort included 40 women and 5 men with a median age of 45.6 years (range, 18–73 years).

After a minimum follow-up of 12 months, 30 patients fulfilled the criteria for RA according to the 1987 ACR criteria.[12] Fifteen patients with polyarthritis did not fulfil the criteria for RA and were classified as Non-RA (used as a control group).

Exclusion criteria included pregnancy or breast-feeding; inability to give informed consent; current use of glucocorticoids, methotrexate, or other disease-modifying anti-rheumatic drugs; active malignancy; cellulites; osteomyelitis; occupation or sports related overuse; trauma; and contraindications to performing an MRI. All patients provided written informed consent, and the study conformed to the ethical principles for medical research involving human subjects according to the World Medical Association Declaration of Helsinki. The study was approved by the ethics committee of Faculdade de Medicina da Universidade de Lisboa.

### Clinical data

Demographic information such as age and sex was collected. The type and distribution of initial joint symptoms, symptoms duration, number of tender and swollen joints of a 28-joint count,[26] and patient's overall disease activity on a visual analogue scale (VAS; range, 0–100 mm) were assessed. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, presence of immunoglobulin M (IgM) rheumatoid factor (RF), and presence of anti-citrullinated protein antibodies (ACPA) were recorded.

Disease activity was assessed by calculating the disease activity score with a 28 joint count (DAS28) for each patient.[27] A diagnosis score for the time of initial presentation was calculated according to the 2010 RA classification criteria of the ACR/EULAR.[10]

**MRI procedure and image evaluation**

MRI examination of the wrists and hands was performed on a 3.0-T device (Magnetom Verio, Siemens Healthcare) using a six-channel surface phased-array body coil including both hands simultaneously in the field of view (FOV); the patient was placed in the prone position with the hands fixed side-by-side over the head with the help of several cushions. The following sequences were acquired before intravenous injection: T1-weighted fast spin-echo sequences on the axial (FOV, 230 mm; slice thickness (ST), 3.5 mm; repetition time (TR)/echo time (TE), 696/31 ms; matrix, 384 × 384; turbo factor (TF), 4; and slice number, 45) and coronal (FOV, 250 mm; ST, 2.0 mm; TR/TE, 583/21 ms; matrix, 384 × 384; TF, 4; and slice number, 24) planes, proton density-weighted fast spin-echo sequence with fat saturation on the coronal plane (FOV, 250 mm; ST, 2.0 mm; TR/TE, 3040/31 ms; matrix, 384 × 384; TF, 10; and slice number, 24), and spectral adiabatic inversion recovery T2-weighted sequence on the sagittal plane (FOV, 250 mm; ST, 3.0 mm; TR/TE, 4950/79 ms; matrix, 384 × 384; TF, 14; and slice number, 28). Intravenous injection of gadolinium (Magnevist®; Bayer HealthCare) at a standard dose of 0.1 mmol/kg (0.2 mL/kg) was performed using an automatic injector with a flow rate of 2.5 mL/s through a 20-G Abbocath® needle into a cubital vein. After injection, a modified T1-weighted fast 3D gradient-echo volumetric interpolated sequence with fat saturation was acquired (FOV, 250 mm; ST, 1.1 mm; section gap, 0.22 mm; TR/TE, 9.29/3.99 ms; matrix, 256 × 256; and flip angle, 10°) by repeated acquisitions starting at 0:00, 0:28, 0:57, 1:26, 1:54, 2:23, 2:52, and 3:20 min post-contrast administration (scanning time, 28 s for each acquisition); the acquisitions were then reconstructed in the coronal (slice number, 43) and axial (slice number, 48) planes at 0:00 min, corresponding to the beginning of contrast injection. T1-weighted fast spin-echo sequences with fat saturation on the axial (FOV, 230 mm; ST, 3.5 mm; TR/TE, 696/31 ms; matrix, 384 × 384; TF, 4; and slice number, 45) and coronal (FOV, 250 mm; ST, 2.0 mm; TR/TE, 777/21 ms; matrix, 384 × 384; TF, 4; and slice number, 24) planes were also acquired after contrast injection.

MRI scoring was performed by MN, 4 years experience fellowship-trained musculoskeletal Radiologist, 9 years cross-sectional image interpretation experienceand included the quantification of synovitis in multiple joints of the hands and wrists (distal radioulnar joint; radiocarpal joint; intercarpal and carpometacarpophalangeal, CMC, joints; metacarpophalangeal, MCP, joints; proximal interphalangeal, PIP, joints; excluding the 1$^{st}$ CMC, the 1$^{st}$ MCP and the 1$^{st}$ PIP). A score of 0 to 3 was assigned for each joint, where 0 was normal with no synovial enhancement and 3 the maximum presumed volume of enhancing tissue in the synovial compartment, according to the RA-MRI score (RAMRIS) defined by Outcome Measures in Rheumatology (OMERACT) imaging studies with validated interobserver intraclass correlation coefficients[28]. Tenosynovitis scoring of post-contrast images on a 0 to 3 scale was performed as described by Haavardsholm et al. with validated interobserver intraclass correlation coefficients [29] but including six tendon groups on the dorsal side of the wrist (extensor pollicis brevis and abductor pollicis longus, extensor carpi radialis brevis and longus, extensor pollicis longus, extensor digitorum and indicis, extensor digiti minimi, and extensor carpi ulnaris) one tendon group on the ventral side of the wrist (flexor digitorium superficialis and profundus) and five tendon groups on the ventral side of the hand (first through fifth flexor tendons at the digit level). Both wrists and hands were included in the quantification. MRI indices for each joint or tendon region (Carpal, carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints; Extensor, all six extensor tendon groups on the dorsal side of the wrist; Flexor, all 6 tendon groups on the ventral side of the wrist and hand; MCP2–5, second through fifth metacarpophalangeal joints; PIP2–5, second through fifth interphalangeal joints) were obtained by adding the left and right scores. MRI counts were calculated after converting region grades to binary variables. Images of 15 patients were blindly rescored at least 2 months after initial evaluation for the purpose of intra-observer reliability calculation.

**Ultrasound procedure and image evaluation**

The joints and tendons of the hands and wrists were examined with a GE Logiq 9® scanner equipped with a multifrequency (8 - 12 MHz) linear array transducer. The trained user (MN, 4 years experience fellowship-trained musculoskeletal Radiologist, 9 years cross-sectional image interpretation experience) was blinded to the patient clinical status and the patients were asked not to discuss their symptoms. The scanning method has been previously described [30] and included evaluation of distal radioulnar joint; radiocarpal joint; intercarpal and carpometacarpophalangeal, CMC, joints; metacarpophalangeal, MCP, joints; proximal interphalangeal, PIP, joints; excluding the 1st CMC, the 1st MCP and the 1st PIP). Tendon evaluation included six tendon groups on the dorsal side of the wrist (extensor pollicis brevis and abductor pollicis longus, extensor carpi radialis brevis and longus, extensor pollicis longus, extensor digitorum and indicis, extensor digiti minimi, and extensor carpi ulnaris) one tendon group on the ventral side of the wrist (flexor digitorium superficialis and profundus) and five tendon groups on the ventral side of the hand (first through fifth flexor tendons at the digit level). Synovial hypertrophy was defined as already published [20]. For power Doppler examination, the pulse repetition frequency was adjusted to provide maximal sensitivity at the lowest possible value but avoiding noise level (between 0.7 and 1.3 kHz).

Grayscale US findings of synovitis and power Doppler positivity were quantified on a 0 to 3 scale for each joint and tendon as previously described [20]. Greyscale and greyscale plus power Doppler indices for each joint or tendon region (same regions as described on MRI image evaluation section) were obtained by adding the left and right scores. US counts were calculated after converting region grades to binary variables. Images of 15 patients were blindly rescored at least 2 months after initial evaluation for the purpose of intra-observer reliability calculation.

**Performance of the 2010 ACR/EULAR criteria in identifying RA patients**

Evaluation of the performance of the 2010 ACR/EULAR criteria for identifying RA patients at baseline was conducted. The diagnostic accuracy was tested again by correcting clinical joint counts with the MRI or US joint and tendon counts. The group of ERA patients was divided by its median in terms of US joint and tendon count and the performance of the 2010 ACR/EULAR criteria for identifying RA patients was further evaluated in each of the subgroups.

**Statistical analysis**

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Baseline characteristics were described as proportions for categorical variables and median (interquartile range) values for continuous variables. All continuous variables were tested for normality with the Kolmogorov-Smirnov test. The Mann-Whitney test was used for paired comparisons.

The difference between the proportions of synovitis in the different groups was tested by the chi-square test. The diagnostic performance of US and MRI was evaluated using receiver operating curve (ROC) analysis. Z statistic was used for pairwise comparison of ROC curves.

Possible associations between synovitis for each group of joints and tendons and RA diagnosis at 12 months were tested by univariate logistic regression analysis. Univariate associations with a p value of 0.05 or less were included in the multivariate analysis. The final multivariate model was obtained by forward procedure. The diagnostic performance of the ACR/EULAR RA classification criteria for the diagnosis of RA at baseline evaluation [10] was tested using ROC analysis. The diagnostic accuracy was tested again by correcting clinical joint counts with the MRI or US joint and tendon counts and after dividing the group of ERA patients by its median in terms of US joint and tendon counts. Z statistic was used for pairwise comparison of ROC curves.

The intra-reader reliability was assessed using Cohen's kappa (k) statistics. Values of k <0.20 were considered to reflect poor agreement, 0.21 - 0.40: fair, 0.41 - 0.60: moderate, 0.61 – 0.80: good, >0.81: excellent.

All tests were two-sided and p values of 0.05 or less were considered statistically significant.

## RESULTS

### Cohort characteristics

The demographic clinical and imaging characteristics of the 45 patients at baseline are shown in Table 1 and are divided into groups according to their diagnoses at the 12-month follow-up. 30 patients fulfilled the criteria for RA according to the 1987 ACR criteria. [12] Fifteen patients with polyarthritis did not fulfil the criteria for RA and were classified as Non-RA.

The Non-RA group included one patient with systemic lupus erythematosus, one patient with psoriatic arthritis, two with fibromyalgia and 11 with undifferentiated arthritis (5 cases of which were self-limited).

### Ultrasound and Magnetic Resonance Identification of Synovitis in ERA patients

Carpal, metacarpophalangeal and proximal interphalangeal joint synovitis was found in 86.7%, 76.7% and 86.7% of patients on MRI compared with 63.3%, 43.3% and 53.3% on US, respectively. Tenosynovitis of the extensor and flexor tendons was found in 66.7% and 86.7% of patients on MRI compared with 40% and 50% on US, respectively. All the differences were statistically significant (Table 2; Figure 1).

### Diagnostic Performance of Ultrasound and Magnetic Resonance

Evaluation of the performance of US and MRI of the different joint and tendon regions for identifying RA patients revealed that MRI had the highest AUC for the different regions, although the difference was not statistically significant for the metacarpophalangeal and proximal interphalangeal joints. MRI and US total counts revealed a good performance of both techniques although MRI had a statistically significantly better performance than US (AUC = 0.959 and AUC = 0.853, respectively; z statistics = 2.210, p = 0.0271) (Table 3).

### Comparison of the median synovitis scores by joint and tendon groups and the association between baseline MRI and US findings and 12-month RA diagnosis

A comparison of the median values of the synovitis scores by groups of joints and tendons between ERA patients and Non-RA patients is presented in Table 4 for each of the imaging techniques. Associations between baseline synovitis by joint and tendon groups and RA diagnosis at 12 months were tested for MRI and US by univariate and multivariate logistic regression analysis.

With the exception of proximal interphalangeal joints and extensor tendons synovitis, all the variables were associated with progression to RA on univariate analysis.

Carpal joint synovitis (OR = 3.64) and tenosynovitis of the flexor tendons (OR = 5.09) as identified by MRI were the most powerful predictors of evolution towards RA on the multivariate logistic regression model.

MRI is a better predictor of RA than US when considering the total joint and tendon counts (OR = 2.769; p = 0.012) (Figure 2.).

**Performance of the 2010 ACR/EULAR criteria in identifying RA patients**

Evaluation of the performance of the 2010 ACR/EULAR criteria for identifying RA patients at baseline, revealed that the use of the criteria as previously described [15] or with US or MRI correction of clinical joint counts resulted in a higher AUC if MRI was taken into consideration (AUC = 0.989) although there was no statistically significant difference in the pairwise comparison of ROC curves (a tendency towards a difference was observed for the comparison ACR/EULAR versus MRI ACR/EULAR, with a p value of 0.048). ERA patients were divided in two groups by its median in terms of US joint and tendon count; in the group of patients with US joint and tendon counts ≤ 10 a statistically significant difference was found between the AUC of the ACR/EULAR criteria as previously described and the AUC of the MRI corrected ACR/EULAR criteria (0.898 versus 0.986; z statistics = 2.181, p = 0.029) (Table 5; Figure 3).

**Reliability**

The intra-reader agreement was good for US (k=0.792) and excellent for MRI (k=0.870).

**DISCUSSION**

Our study identified a significantly higher prevalence of joint and tendon synovitis by MRI in comparison to US in an early RA cohort. We also demonstrated a significantly better diagnostic performance of 3-T MRI in comparison to US for RA diagnosis. In this 1-year follow-up study we additionally found that synovitis of the radiocarpal joint and tenosynovitis of the flexor tendons as identified by MRI were independent predictors of progression to RA.

In face of recent scientific evidence that tenosynovitis identification may be of critical value for the diagnosis of early RA [23, 31-33] our study included joint but also tendon evaluation at multiple hand and wrist territories. In fact, the reported prevalence of tenosynovitis in established RA was mainly based on clinical examination varying from 5% to 55% [34]. The available published data on patients with established RA comparing US with MRI reported tendon sheath widening in 34% of flexor tendons and 10% of extensor tendons by MRI compared with 21% and 5%, respectively, using US [35]. In untreated early RA the work by Wakefield et al. [23] comparing both techniques demonstrated a high frequency of flexor tenosynovitis occurring in 57 (28.5%) of 200 joints in 24 (48%) of 50 patients on US compared with 128 (64%) of 200 joints in 41 (82%) of 50 patients on MRI. Extensor tenosynovitis was found in 14 (7%) joints of 9 (18%) patients on US compared with 80 (40%) joints of 36 (72%) patients on MRI. MRI revealed an increased sensitivity in comparison to US. These results are in line with our work that also demonstrated a significantly higher percentage of patients with tenosynovitis identified by MRI in comparison to US.  However, our work suggest a slightly higher prevalence of tenosynovitis in early RA (flexor tenosynovitis in 15 (50%) of 30 patients on US compared with 26 (86.7%) of 30 patients on MRI and extensor tenosynovitis in 12 (40%) of 30 patients on US compared with 20 (66.7%) of 30 patients on MRI). The relevance of tenosynovitis identification by MRI is highlighted by our finding of a better diagnostic performance of flexor and extensor tenosynovitis as identified by MRI for the diagnosis of RA in comparison to US identification. The multivariate logistic regression model identified flexor tenosynovitis recognised by MRI as one of the most powerful predictors of RA (OR = 5.099).  Ultrasonographic evaluation of minor degrees of tenosynovitis is known as challenging.[36] The use of 3-T MRI has high field strength, signal-to-noise ratio and image quality [37-41, 42] and is known to provide precise and complete morphological analysis of the hands and wrists [43] justifying its better performance as compared to US.

In respect to joint synovitis the available comparative study by Terslev et al. [44] concludes that estimates of synovial inflammatory activity by Doppler US and postcontrast MRI were comparable. However, the main focus of the study was the comparison of synovial inflammatory activity parameters and not the presence versus absence of synovitis. In addition, the study was conducted in patients with established RA, restricting the comparison with our results. Even so, the finding of a 75% agreement between the 2 imaging modalities and a moderate k value of 0.45 on that work leaves space for questioning which imaging modality is the best for identifying the presence of synovitis on an individual joint or tendon basis. In a study with 46 patients with recently diagnosed RA (onset within 2 years) by Hoving et al. [22] the percentage of participants with joint synovitis at baseline was higher by MRI in comparison to US evaluation (71.7% versus 54.3%). These findings are in line with our results, which document a higher proportion of synovitis detection by MRI. Our results revealed carpal synovitis to be present in 19 (63.3%) out of 30 patients on US compared with 26 (86.7%) out of 30 patients on MRI. There is a better diagnostic performance of carpal synovitis as identified by MRI for the diagnosis of RA in comparison to US identification (MRI AUC = 0.890 versus US AUC = 0.757; z statistics = 2.473; p = 0.0134); the multivariate logistic regression model identified carpal synovitis recognised by MRI as one of the most powerful predictors of RA (OR = 3.641; p = 0.032).

Consideration of the total joint and tendon count revealed a good diagnostic performance of both MRI (AUC = 0.959; p = 0.000) and US (AUC = 0.853; p = 0.000), although with a statistically significant better performance of MRI (z statistic = 2.210; p = 0.0271).

We tried to identify a strategy by which MRI and US joint and tendon counts could contribute to improvement of the diagnostic performance of the 2010 ACR/EULAR RA classification criteria.[10] The mean initial ACR/EULAR score in our ERA cohort was less than 6, confirming that some patients were not being identified as having RA at the time of presentation by the new criteria. Our results are in agreement with those from recent studies highlighting that despite improved performance of the 2010 criteria, over- and under-diagnosis may still remain important issues in early arthritis and that the new criteria may fail to identify RA patients with symmetrical seronegative arthritis and limited joint involvement.[12, 45, 16] In fact, in our ERA cohort, taking into consideration the group of patients with US joint and tendon count ≤

10, the ACR/EULAR criteria diagnostic performance in terms of AUC was significantly improved by correcting clinical joint counts with MRI joint and tendon counts (AUC = 0.898 and AUC = 0.986, respectively; z statistic = 2.181, $p < 0.05$). The relevance of MRI correction in this subset of patients is further highlighted by the low performance of the original 2010 ACR/EULAR criteria in this group (AUC = 0.898, p = 0.052). Despite the better performance of US corrected ACR/EULAR criteria in the same group in comparison with the criteria as previously described, the difference was not statistically significant (AUC = 0.930 and AUC = 0.898, respectively; ns). On the other hand, if we take into consideration the complete cohort of patients or the patients with US joint and tendon count > 10, there was no statistically significant improvement of the 2010 ACR/EULAR performance. Our findings suggest that there is a specific subset of patients which can benefit from MRI joint and tendon counts and this should be explored in a larger cohort.

One of the strengths of our study was the bilateral evaluation by both US and MRI. This was critical for a precise evaluation of the inflammatory burden and for determination of the diagnostic potential of each technique. In fact, previous clinical and MRI descriptions of early RA depicted asymmetric joint involvement in 30–94% of patients and symmetrisation only occurring after significant RA progression [46, 47, 15, 48-51].

There are also some limitations in our study. We have not studied bone erosions or bone oedema. However bone oedema is a strict MRI finding and US has low sensitivity for bone erosions, hindering comparison between techniques. In addition, proliferation of the synovium is one of the earliest changes in RA and bone erosions represent a late stage in the disease process. Thus, we focused our comparative study on synovitis evaluation. Besides, the sample size of our study was modest, only 45 patients. This fact was related to the strict inclusion criteria, namely disease duration, polyarthritis involvement, no previous treatments and the prospective nature of the study. However, we believe that the homogeneity of the groups in the study mitigated this fact.

In conclusion, our data confirm that MRI identifies a higher prevalence of synovitis in comparison to US in an early arthritis cohort. In addition, our study identifies both techniques as good diagnostic performers in respect to RA diagnosis, although MRI reveals a significantly higher diagnostic capability. Synovitis of the carpal joints and of the flexor tendons as identified by MRI were the most powerful predictors of evolution towards RA. In patients with US joint and tendon counts ≤ 10, MRI can improve the diagnostic performance of the 2010 ACR/EULAR classification criteria.

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**COMPETING INTERESTS**

The authors have no conflicts of interest to declare.

**AUTHOR'S CONTRIBUTIONS**

MN was responsible for the conception and design of the study, acquisition, analysis and interpretation of data and drafting of the manuscript.

CR and JAPS were responsible for data acquisition.

AMR was responsible for acquisition, analysis and interpretation of data.

JEF, JC and HC were responsible for critical revision of the article for important intellectual content and final approval of the version to be published.

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FIGURE LEGENDS

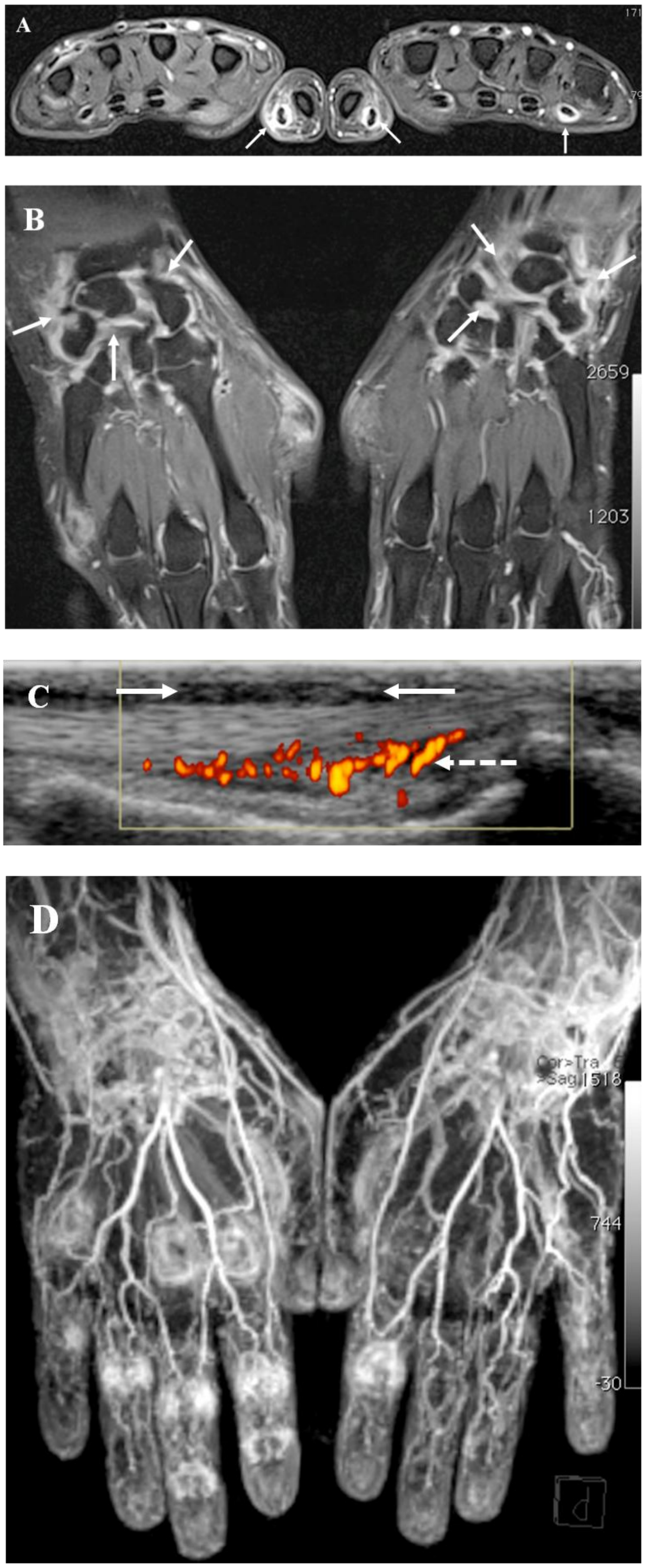

**Figure 1** Bilateral magnetic resonance imaging (MRI) and ultrasound (US) of the hand and wrist of a 49-year-old woman with early inflammatory arthritis with a disease duration of 9 months; she fulfilled the criteria for rheumatoid arthritis at presentation. (A) Axial T1 fat-sat sequence after intravenous contrast administration showing grade 2 (≥2 and <5 mm synovial proliferation with enhancement) tenosynovitis of the flexor tendons of the first digit on the right and of the first and fifth digits on the left (arrows). (B) Coronal T1 fat-sat sequence after intravenous contrast administration demonstrating enhancement of bilateral carpal joint synovitis (arrows). (C) Ultrasound examination of the fifth digit on the left demonstrating tenosynovitis (arrows) and active power doppler signal (dashed arrows). (D) Maximum intensity projection of a 3D digitally subtracted dataset of the VIBE acquisition after contrast administration, demonstrating increased vascularity of synovitis of carpal, metacarpophalangeal and interphalangeal joints. The tube-like appearance of digit tenosynovitis is also clearly depicted.

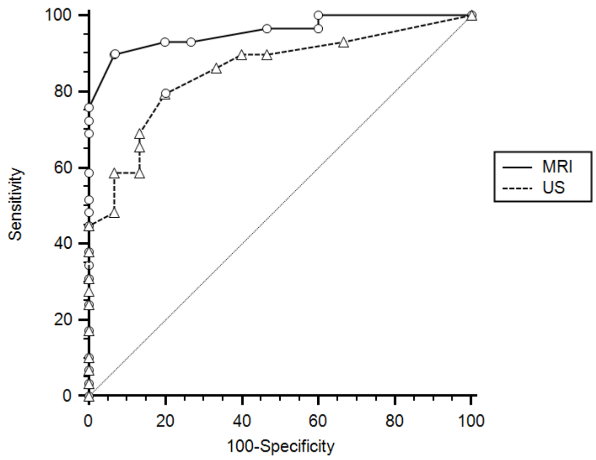


**Figure 2** ROC curve of the diagnostic performance of total Ultrasound and Magnetic Resonance Imaging joint and tendon count for identifying RA (AUC, 0.853; 95% CI, 0.740-0.966 for US and AUC, 0.959; 95% CI, 0.857-1.000 for MRI).

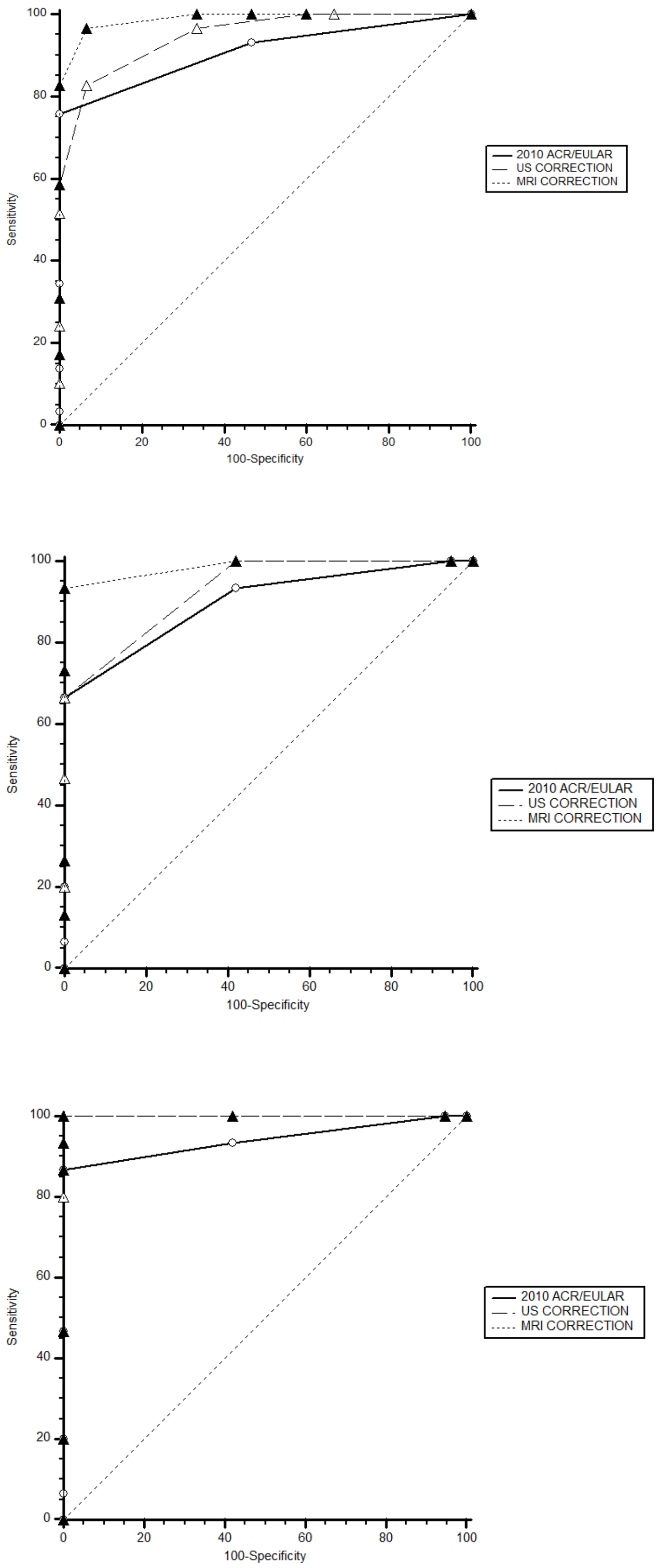


**Figure 3** ROC curves using ACR/EULAR criteria as previously described [15] for identifying RA patients (—), US corrected ACR/EULAR (---) and MR corrected ACR/EULAR (•••). Curves are presented for the

complete group of ERA patients (A) and for ERA patients with with US joint and tendon counts $\leq 10$ (B) and $> 10$ (C).

**TABLES**

**Table 1.** Demographic, clinical, laboratory, US and MR data of patients at baseline

| Characteristic | ERA (n = 30) | Non-RA (n = 15) |
|---|---|---|
| Number (men/women) | 0/30 | 5/10 |
| Age (y)* | 51.0 (21.0) | 38.0 (10.0) |
| Disease duration (mo) | 5.0 (6.0) | 7.0 (5.0) |
| Tender joint count[a]* | 8.0 (11.0) | 3.0 (3.0) |
| Swollen joint count[a]* | 4.0 (6.0) | 1.0 (1.5) |
| ESR (mm/h)* | 28.0 (24.0) | 6.0 (8.0) |
| Overall disease activity (VAS) | 60.0 (30.0) | 60.0 (29.0) |
| DAS28* | 5.19 (1.61) | 3.3 (0.8) |
| MRI joint and tendon index* | 22 (15.0) | 3.0 (4.5) |
| MRI joint and tendon counts* | 13.0 (11.0) | 3.0 (4.5) |
| US (GS) joint and tendon index* | 10.0 (14.0) | 2.0 (7.0) |
| US (GS) joint and tendon counts* | 7.0 (9.0) | 2.0 (5.0) |
| US (GS-PD) joint and tendon index* | 11.0 (18.0) | 2.0 (8.0) |
| US (GS-PD) joint and tendon counts* | 8.0 (11.0) | 2.0 (5.5) |
| ACR/EULAR* | 5.0 (2.0) | 2.0 (0.5) |

Except where indicated, the values are median (IQR)

Mann-Whitney U test; * represents $p < 0.05$

[a]from 28-joint count

Greyscale, greyscale plus power Doppler and MRI indices for each joint or tendon region (as described in the material and methods section) were obtained by adding the left and right scores. US counts were calculated after converting region grades to binary variables.

ACR/EULAR, score for RA according to the 2010 American College of Rheumatology/European League against Rheumatism classification criteria; DAS28, 28-joint disease activity score; ERA, early rheumatoid arthritis; ESR, erythrocyte sedimentation rate; GS, greyscale ultrasound; MR, magnetic resonance; PD, power Doppler ultrasound; RA, rheumatoid arthritis; US, ultrasound; VAS, visual analogue scale.

**Table 2**. Proportion of ERA patients with synovitis or tenosynovitis as identified by US or MRI in the different joint and tendon regions

| Characteristic | US (n = 30) | MRI (n = 30) | p value* |
|---|---|---|---|
| Carpal | 19 (63.3%) | 26 (86.7%) | **0.037** |
| MCP2-5 | 13 (43.3%) | 23 (76.7%) | **0.000** |
| PIP 2-5 | 16 (53.3%) | 26 (86.7%) | **0.005** |
| Extensor | 12 (40%) | 20 (66.7%) | **0.038** |
| Flexor | 15 (50%) | 26 (86.7%) | **0.002** |

*Chi-square test; p values given in bold are significant.

Carpal, carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints; Extensor, six extensor tendon groups on the dorsal side of the wrist, as described in the Methods section; Flexor, six tendon groups on the ventral side of the wrist and hand, as described in the Methods section; MCP2–5, second through fifth metacarpophalangeal joints; MRI, magnetic resonance imaging; PIP2–5, second through fifth interphalangeal joints; US, ultrasound.

**Table 3**. Performance of Ultrasound and Magnetic Resonance Imaging for identifying RA patients

| Synovitis | AUC | 95% CI | | p value | z statistic (p-value) |
|---|---|---|---|---|---|
| | | Lower Bound | Upper Bound | | |
| MRI Carpal | 0,890 | 0,793 | 0,987 | **0,000** | 2,473 (**0,0134**) |
| US Carpal | 0,757 | 0,616 | 0,897 | **0,005** | |
| MRI MCP2-5 | 0,817 | 0,692 | 0,941 | **0,001** | 1,860 (**0,0628**) |
| US MCP2-5 | 0,702 | 0,548 | 0,856 | **0,028** | |
| MRI PIP 2-5 | 0,714 | 0,548 | 0,881 | **0,020** | 1,407 (0,1596) |
| US PIP2-5 | 0,567 | 0,396 | 0,737 | 0,470 | |
| MRI Extensor | 0,813 | 0,684 | 0,942 | **0,001** | 2,606 (**0,0092**) |
| US Extensor | 0,706 | 0,556 | 0,855 | **0,026** | |
| MRI Flexor | 0,926 | 0,846 | 1,000 | **0,000** | 3,817 (**0,0001**) |
| US Flexor | 0,731 | 0,586 | 0,876 | **0,012** | |
| Total MRI | 0,959 | 0,857 | 1,000 | **0,000** | 2,210 (**0,0271**) |
| Total US | 0,853 | 0,740 | 0,966 | **0,000** | |

The presented data refers to MRI and US (GS-PD) counts.

p values given in bold are significant.

z statistic results from pairwise comparison of ROC curves (US versus MRI)

AUC, area under the receiver operating characteristic curve; Carpal, carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints; CI, confidence interval; Extensor, six extensor tendon groups on the dorsal side of the wrist, as described in the Methods section; Flexor, six flexor tendon groups on the ventral side of the wrist and hand, as described in the Methods section; GS, greyscale ultrasound; PD, power Doppler ultrasound; MCP2–5, second through fifth metacarpophalangeal joints; MRI, magnetic resonance imaging; PIP2–5, second through fifth interphalangeal joints; US, ultrasound.

**Table 4.** Comparison of the median (IQR) value of synovitis scores for ERA and NON-RA patients and the association between baseline MRI and US findings and 12-month RA diagnosis (univariate and final multivariate logistic regression models): Joint and tendon analysis by region

| Synovitis | ERA | NON-RA | Univariate logistic regression analysis | | | | Multivariate logistic regression analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | OR ($R^2$) | 95% CI Lower Bound | 95% CI Upper Bound | P (c stat) | OR ($R^2$) | 95% CI Lower Bound | 95% CI Upper Bound | P (c stat) |
| MR Carpal | 3 (4)* | 0 (0.5)* | 3,320 (0.40) | 1,555 | 7,087 | **0,002** (0.890) | 3,641 (0.487; 0.596) | 1,119 | 11,841 | **0,032** (0.979) |
| US Carpal | 2 (2)* | 0 (1)* | 2,288 (0.21) | 1,159 | 4,517 | **0,017** (0.757) | | | | |
| MR MCP2-5 | 2 (3)* | 0 (0)* | 3,136 (0.29) | 1,353 | 7,268 | **0,008** (0.817) | | | | |
| US MCP2-5 | 0 (3)* | 0 (0)* | 1,648 (0.15) | 1,026 | 2,647 | **0,039** (0.702) | | | | |
| MR PIP 2-5 | 3 (3)* | 1 (3.5)* | 1,650 (0.16) | 1,108 | 2,455 | **0,014** (0.714) | | | | |
| US PIP 2-5 | 1 (3)* | 2 (3)* | 1,192 (0.03) | ,861 | 1,651 | 0,289 (0.567) | | | | |
| MR Extensor | 1 (2)* | 0 (0)* | 6,330 (0.30) | 1,602 | 25,012 | **0,008** (0.813) | | | | |
| US Extensor | 0 (2) | 0 (0) | 2,764 (0.18) | ,953 | 8,017 | 0,061 (0.706) | | | | |
| MR Flexor | 4 (3)* | 0 (0)* | 4,373 (0.49) | 1,802 | 10,609 | **0,001** (0.926) | 5,099 (0.487; 0.596) | 1,620 | 16,051 | **0,005** (0.979) |
| US Flexor | 1 (3)* | 0 (0)* | 1,984 (0.19) | 1,102 | 3,571 | **0,022** (0.731) | | | | |
| Total MR | 13 (11) * | 3.0(4.5) * | 1,996 (0.54) | 1,237 | 3,221 | **0,005** (0.959) | 2,769 (0.544) | 1,249 | 6,139 | **0,012** (0.959) |
| Total US | 7 (9) * | 2.0 (5.0) * | 1,356 (0.33) | 1,108 | 1,659 | **0,003** (0.853) | 0,727 (0.544) | 0,445 | 1,186 | 0,201 (0.959) |

The presented data refers to MRI and US (GS-PD) counts.

Mann-Whitney U test; * represents $p < 0.05$.

Univariate and final multivariate logistic regression analysis; cstat, c statistic; OR, odds ratio; 95% CI, 95% confidence interval; R2, Cox & Snell R square. p values given in bold are significant.

Carpal, carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints; ERA, early rheumatoid arthritis; Extensor, six extensor tendon groups on the dorsal side of the wrist, as described in the Methods section; Flexor, six flexor tendon groups on the ventral side of the wrist and hand, as described in the Methods section; GS, greyscale ultrasound; PD, power Doppler ultrasound; MCP2–5, second through fifth metacarpophalangeal joints; MR, magnetic resonance; PIP2–5, second through fifth interphalangeal joints; RA, rheumatoid arthritis.

**Table 5.** Performance of the ACR/EULAR criteria for identifying RA patients

| Criteria | Value | AUC | 95% CI | p* | z statistic (p) |
|---|---|---|---|---|---|
| All Patients (n=30) | | | | | |
| ACR/EULAR | 5.0 (2.0) | 0.909 | 0.783-0.975 | **0.040** | # 1.974 (0.048) |
| US ACR/EULAR | 7.0 (2.0) | 0.948 | 0.836-0.992 | **0.028** | - |
| MRI ACR/EULAR | 7.0 (2.0) | 0.989 | 0.898-1.000 | **0.009** | # 1.974 (0.048) |
| US ≤ 10 (n=15) | | | | | |
| ACR/EULAR | 5.0 (1.0) | 0.898 | 0.746-0.975 | 0.052 | ‡ 2.181 (**0.029**) |
| US ACR/EULAR | 5.0 (2.0) | 0.930 | 0.787-0.989 | **0.032** | - |
| MRI ACR/EULAR | 6.0 (1.0) | 0.986 | 0.872-1.000 | **0.014** | ‡ 2.181 (**0.029**) |
| US > 10 (n=15) | | | | | |
| ACR/EULAR | 5.0 (1.0) | 0.940 | 0.802-0.993 | **0.047** | - |
| US ACR/EULAR | 7.0 (1.0) | 1.000 | 0.897-1.000 | **0.000** | - |
| MRI ACR/EULAR | 7.0 (1.0) | 1.000 | 0.897-1.000 | **0.000** | - |

ACR/EULAR value is presented as median (IQR)

*ROC analysis.

z statistic results from pairwise comparison of ROC curves (ACR/EULAR versus US ACR/EULAR versus MRI ACR/EULAR); ‡, represents a pairwise comparison with statistically significant association; #, represents a tendency.

ACR/EULAR, performance of ACR/EULAR score for identifying RA patients; US ACR/EULAR, performance of ACR/EULAR score for identifying RA patients, with correction of the clinical joint counts by the US joint and tendon counts; MRI ACR/EULAR, performance of ACR/EULAR score for identifying RA patients, with correction of the clinical joint counts by the US joint and tendon counts.

US ≤ 10, patients with US joint and tendon counts ≤ 10; US > 10, patients with US joint and tendon counts > 10.

ACR/EULAR, American College of Rheumatology/European League against Rheumatism; AUC, area under the receiver operating characteristic curve; MRI, magnetic resonance imaging; US, ultrasound.

# DISCUSSION

Identifying individuals at high risk of developing RA as soon and as precisely as possible and initiating an appropriate antirheumatic therapy has become a critical objective for the management of early inflammatory arthritis.

Despite this clinical trend, most of the previous research on imaging in RA focused on established disease, with evaluation of the dominant or clinically most affected hand. In this way, the contribution of imaging techniques for early diagnosis of RA and the relative contribution of each method remain largely unknown.

We believe that imaging modalities like P-DUS and D-MRI enabling early detection and monitoring of synovitis, and providing information on disease activity, could have an impact on the identification of individuals with early undifferentiated arthritis who will develop RA, allowing individualized decisions regarding early and intensive treatment.

The aim of this thesis was to identify with new imaging techniques, P-DUS and D-MRI, findings that predict progression to RA in patients presenting with early inflammatory arthropathy.

In the Part I of our thesis we evaluated rapidly acquired serial images after administering intravenous gadolinium with a D-MRI protocol directed to both wrists and hands in patients presenting with early arthritis. The possibility of obtaining functional MRI data that translates into information in respect to disease activity in early arthritis could constitute a major clinical finding. Adding this information to the structural findings that are possible in the same MRI examination opens the window of a comprehensive patient examination with only one test.

Previous studies showed correlation between D-MRI parameters and clinical findings and treatment effects; however, all these studies were performed with low-field MRI using quite complex formulae for enhancement quantification and using patients with established RA [83-91, 167-174]. We used a standardized infusion technique, in an attempt that changes in the local diffusion of the contrast agent were related to the number, size and permeability of the synovial vessels. We used a dedicated protocol that strictly includes both hands in the FOV for a more precise quantification of the disease process; this enabled accurate determination of RAMRIS score for both hands compared to the previous studies that included only the dominant hand [167-174]. The option of including both hands in the FOV hinders the use of the dedicated hand and wrist coil. However, the image quality was not negatively affected because the surface coil performed extremely well owing to the greater field strength at 3-T with its high signal-to-noise and contrast-to-noise ratios [175], and the use of the VIBE sequence. Despite the relatively long acquisition time (28 s), the VIBE sequence obtained in this study had a higher temporal resolution than those obtained with some of the previously described dynamic protocols (acquisition times between 10–48 s). In fact, the lowest acquisition times in previous studies correspond to low spatial resolution, small FOV, or limited slice number [171, 172, 176-178]. The nearly isotropic resolution of this sequence allowed careful selection of an area of synovial tissue for the dynamic study by drawing a small circular ROI precisely in the areas of progressive and late maximal enhancement. Anyway, we believe that future research should focus on high resolution sequences with shorter acquisition times.

We found that RE, REE, and RAMRIS score for synovitis were significantly correlated to DAS28 score, suggesting that these parameters, even in early disease, can reflect the actual degree of joint inflammation and disease activity. The use of both hands for the RAMRIS quantification of synovitis as opposed to the previously validated technique using only the dominant hand was probably responsible for the highly significant correlation between this parameter and DAS28 score. Using our method, even minor degrees of inflammation can be considered. However, one limitation of one of our parameters (RE) is the lack of a rate character; this raises concerns regarding the reproducibility of dynamic MRI on different scanners and should be considered on future studies.

In light of our finding of a precise correlation between DAS28 score and MRI parameters of disease activity at 3-T, we also identified a cutoff value for MRI measurements that can identify patients with active disease. To the best of our knowledge this was never described in early disease and could contribute for a better patient management, by providing information on disease activity in addition to structural lesion.

The part II of our thesis identified tenosynovitis as a discriminating factor of evolution towards RA in patients with arthritis for less than 3 month's duration. Tenosynovitis of the wrists and hands has received little attention in previous literature. In fact, there is no OMERACT RAMRIS [179] definition of the term 'tenosynovitis' and despite the proposal of an MRI tenosynovitis score for established disease[180], its use has been sparse, highlighting the relevance of our results.

Tenosynovitis of the extensor carpi ulnaris, of the flexor tendons of the second finger and of the flexor tendons as a group and radiocarpal joint synovitis, were recognised as significantly associated with progression to RA in patients with disease duration of less than 3 months. Even in patients with longer disease duration (3–12 months), tenosynovitis of the flexor tendons of the second finger remained one of the significant discriminating features for fulfilling RA criteria. A previous study had already identified flexor tenosynovitis of the hand as a strong predictor of early RA. However, that work was performed with a low-field-strength extremity MRI unit and included patients with disease durations up to 24 months [181], which exceeds the currently accepted definitions of early RA [182, 183]. The other reports on the study of tendons by MRI have either focused on predicting tendon rupture in early RA or assessed established long standing disease.[184-188] In this way, our work represents the first MRI documentation of the relevance of tenosynovitis in early RA, suggesting that tenosynovitis is one of the first markers of RA and might manifest prior to joint synovitis, which seems to be more evident later in the disease course. Actually, in face of these results, we may speculate that clinical examination in terms of painful joint count in early arthritis might in fact have a major contribution from tenosynovitis.

We also tried to identify a strategy by which tenosynovitis could contribute to improvement of the diagnostic performance of the 2010 ACR/EULAR RA classification criteria.[189] In fact, the mean ACR/EULAR score in our VERA and ERA cohort was less than 6, confirming that some patients were not being identified as having RA at the time of presentation by the new criteria. This is in line with recent works that confirm that the 2010 ACR/EULAR RA classification criteria may still lead to significant over- and under-diagnosis within the first 3 months after the onset of symptoms [67. 68]. In our cohort of

RA patients, the ACR/EULAR criteria diagnostic performance in terms of AUC was improved by the addition of one score point to each patient with at least one of the most significant tendons affected by synovitis. This finding, by allowing a better classification of early RA patients and an improvement of the ACR/EULAR diagnostic performance by the use of a new and previously unexplored imaging parameter may have a major impact in early diagnosis and deserves to be tested in large trials.

Previous clinical descriptions of early RA depicted an increased prevalence of asymmetric joint involvement. However there is a high disparity in the results of different clinical studies, with documentation of asymmetry in 30–94% of joints [190-196]. In our bilateral MRI study, joint asymmetry rates 80% in VERA patients and 69.3% in ERA patients were detected. These findings provide a morphological confirmation that early RA may be an asymmetrical disease and suggest a tendency towards symmetry as the disease progresses from VERA to ERA. These findings should be taken in close consideration in patient evaluation in the future, namely on MRI studies, by clearly avoiding unilateral evaluation.

The part III of our study was dedicated to inter-technique comparison considering our global early RA cohort (patients with less than one year disease duration). In face of the recent tendency towards the use of modern imaging modalities in RA, the comparative evaluation of the diagnostic performance and determination of the added value of each technique could have a critical role in patient management.

Our study included joint but also tendon evaluation at multiple hand and wrist territories. The available published data on patients with established RA comparing US with MRI reported a higher prevalence of tendon sheath widening by MRI than using US [197-202]. The only available study with untreated early RA comparing both techniques in respect to tendon evaluation [197] demonstrated a high frequency of flexor and extensor tenosynovitis, a finding that is in line with our work that also demonstrated a significantly higher percentage of patients with tenosynovitis identified by MRI in comparison to US. The relevance of tenosynovitis identification by MRI is highlighted by our finding of a better diagnostic performance of flexor and extensor tenosynovitis as identified by MRI for the diagnosis of RA in comparison to US identification. In fact, our multivariate logistic regression model identified flexor tenosynovitis recognised by MRI as one of the most powerful predictors of RA. The inclusion of this parameter in future classification models should definitely be considered.

In respect to joint synovitis, a previous study with patients with less than 2 years disease duration identified that the percentage of participants with joint synovitis at baseline was higher by MRI in comparison to US evaluation [164]. These findings are in line with our results in early RA patients, which document a higher proportion of joint synovitis detection by MRI; the multivariate logistic regression model identified carpal synovitis recognised by MRI as one of the most powerful predictors of RA. Our results confirm MRI as the best imaging tool for joint synovitis evaluation and this fact should be taken into account on future classification models.

The evaluation of the diagnostic performance of both MRI and US when we took into consideration the total joint and tendon count, revealed a good diagnostic performance of both MRI and US, although with a statistically significant better performance of MRI, a finding that reinforces the global potential of the technique as a diagnostic tool.

We also aimed to identify a strategy to ascertain which technique, MRI or US, could better contribute to improve the diagnostic performance of the 2010 ACR/EULAR RA classification criteria [199], by correcting clinical joint counts with imaging joint and tendon counts. We found that in our global early RA cohort, if we took into consideration the group of patients with US joint and tendon count ≤ 10, the ACR/EULAR criteria diagnostic performance in terms of AUC was significantly improved by correcting clinical joint counts with MRI joint and tendon counts. The clinical relevance of MRI correction in this subset of patients is further highlighted by the low performance of the original 2010 ACR/EULAR criteria in this group. On the other hand, if we took into consideration the complete cohort of patients or the patients with US joint and tendon counts > 10, there was no statistically significant improvement of the 2010 ACR/EULAR performance with MRI correction. Our results suggest that there is a specific subset of patients which can benefit from MRI joint and tendon counts. These are extremely relevant findings as they indicate that patients presenting with early arthritis and a 2010

ACR/EULAR score < 6, in the case of US joint and tendon count ≤ 10, should receive MRI evaluation for imaging correction of clinical joint counts.

# CONCLUSION

In conclusion, our findings support the use of D-MRI for quantification of disease activity and for discriminating active disease from inactive disease in early polyarthritis.

Our data also confirm that tenosynovitis of the extensor carpi ulnaris, of the flexor tendons of the second finger and of the radiocarpal joint are common MRI findings in very early RA. In addition, our study identifies early RA as an asymmetrical disease, suggesting the importance of a bilateral acquisition protocol.

We additionally found that MRI identifies a higher prevalence of synovitis in comparison to US in an early arthritis cohort. Our study identifies both techniques as good diagnostic performers in respect to RA diagnosis, although MRI reveals a significantly higher diagnostic capability. Synovitis of the carpal joint and of the flexor tendons as identified by MRI were the most powerful predictors of evolution towards RA. In patients with US joint and tendon counts ≤ 10, MRI correction of clinical joint counts can improve the diagnostic performance of the 2010 ACR/EULAR classification criteria.

Our results allow us to state that bilateral US and MRI evaluation of the hands and wrists in early inflammatory arthritis can contribute for an early identification of RA patients. Identifying individuals at high risk of developing RA as soon and as precisely as possible is known as critical for the initiation of appropriate anti-rheumatic therapy.

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