What Are the Potential Roles Magnetic Resonance Imaging Can Play in Differentiated and Undifferentiated Arthritis?

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ABSTRACT

Magnetic resonance imaging (MRI) has advanced our understanding of many types of arthritis, with respect to both inflammatory processes and articular damage. The role of MRI in differentiating between different forms of arthritis is still debatable and under discussion. The current available data suggest that MRI can separate subsets of early synovitis patients on the basis of two principal imaging patterns: one in which the inflammatory changes are located primarily in the synovium; and another in which the periarticular entheses are inflamed in association with intense edema of the adjacent bone. These two patterns are proposed to broadly classify patients with early synovitis into an “RA” phenotype where synovitis is the primary process, and a “spondyloarthropathy” (SpA) phenotype where enthesitis is the primary process and synovitis occurs on a secondary basis. Enthesitis is a common feature on MRI in SpA, which can help to determine the evolving pattern of patients with undifferentiated arthritis of the knee joint, and may have important clinical implications for classification purposes.

Keywords: enhanced magnetic resonance imaging (MRI), undifferentiated arthritis, knee enthesitis, rheumatoid arthritis, seronegative spondylarthropathy (SpA)

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UNDIFFERENTIATED ARTHRITIS “THE OLD AND THE NEW CONCEPT”

In rheumatology practice, most patients who present with recent-onset arthritis have undifferentiated arthritis (UA), which is a form of arthritis that does not fulfill the classification criteria for a more definitive diagnosis. Based on results from several inception cohort studies, it is known that 40–50% of patients with UA experience spontaneous remission, whereas rheumatoid arthritis (RA) develops in one-third of patients [1].

It has been stated that the term “undifferentiated” could have any of the following implications: (1) an early stage of a well-defined rheumatic disease that will later become differentiated; (2) an abortive form of a well-defined rheumatic disease; (3) an overlap syndrome; or (4) a truly unknown, undefined disease that may be differentiated in the future. Of note, none of these classifications infers a pathogenic mechanism [2]. A problem with the expression “UA” is that it is a non-validated description of a phenotype. In the literature, various definitions and criteria are used for the early phase of arthritis. “Early arthritis”, “early RA”, and “undifferentiated arthritis” are terms that are currently in use to describe either arthritis that might evolve into RA or that has been diagnosed early after the onset of arthritis [3].

The term undifferentiated arthritis is a more appropriate and realistic term to describe those patients in this domain, because not all patients presenting with early-onset UA will evolve into RA. There is a clear need for consensus regarding the meaning of the terms early arthritis and undifferentiated arthritis.

In daily practice, the diagnosis of RA or psoriatic arthritis (PsA) is primarily based on clinical findings and laboratory tests, but sometimes it is difficult to differentiate between RA, PsA, or other chronic inflammatory joint diseases in cases that remain undifferentiated after initial clinical, biochemical, and radiographic evaluation. Moreover, the absence of psoriatic skin lesions does not always exclude the diagnosis of PsA, especially in the absence of other important features of the disease (e.g., finger nail dystrophy, seronegativity for RF, distal interphalangeal joint involvement, oligoarthritis, asymmetry, and dactylitis of the fingers (Figure 1) or toes (Figure 2)) [5].

Symmetrical involvement of the wrists and small joints of the hands and feet is highly characteristic of established RA and,
when present at the onset of the synovitis, it suggests that these symptoms will probably evolve into RA, particularly if RF and anti-CCP antibodies are present. The tendency for PsA to involve the distal interphalangeal joints of the hands, and to involve multiple joints of a single digit asymmetrically, is also used as an early classification feature, even without any obvious psoriatic plaques. The “reactive arthritis” syndrome that follows particular genitourinary and gastrointestinal infections in some individuals typically features an asymmetric lower extremity oligoarthritis. Patients with this articular pattern are often labeled as reactive arthritis, even if a preceding infection cannot be identified. Features such as enthesitis, sacroiliitis, and dactylitis tend to cluster with this complex of articular inflammation, and collectively form an overall “spondylarthritis” pattern [6]. The prognosis of patients with UA may vary from self-limited to severe destructive RA. Because early aggressive treatment might offer an effective means to slow disease progression in RA, it is important to identify UA patients who will develop RA and treat them as early as possible. Although not developed to support the diagnostic process, the American College of Rheumatology (ACR) 1987 revised criteria [7] are commonly used for disease classification. According to these criteria, patients can be classified as having RA when at least four of seven criteria are met using patient history, physical examination, and laboratory and radiographic findings. The classification criteria reach a sensitivity of 90% if patients are observed over a period of several years, but such a cumulative approach has been shown to be insufficient for early diagnosis of RA in patients with arthritis of recent onset [8, 9].

At its October meeting in 2009, the ACR and the European League against Rheumatism (EULAR) released revised guidelines for diagnosis of RA. The revised criteria rate patients on
a scale of 0–10 points, with points assigned in four separate domains of signs and symptoms: joint involvement, serology, duration of symptoms, and acute phase reactants. Those who score 6 or more points in total are considered to have definite RA. The joint ACR/EULAR panel is still considering what score should distinguish patients with probable RA from those in whom RA is unlikely, but this cutpoint will probably be set at 3 or 4 points. The new diagnostic criteria bring official policy on the diagnosis of RA into line with several years of research findings showing that the early initiation of sometimes aggressive therapy can prevent erosions and may occasionally induce remission. This new set of criteria matches the emerging current consensus in which patients with inflammatory arthritis should immediately start treatment with a disease-modifying antirheumatic drug (DMARD).

MRI AND JUSTIFICATION FOR TREATMENT IN EARLY-ONSET UA

Imaging may play an important role in the evaluation of patients with early arthritis. Various imaging methods can help with diagnosis, predict prognosis, and follow disease progression and even response to treatment. Previously, conventional radiography was the principal method used to evaluate and follow bone damage in patients with inflammatory arthritis [10].

In our opinion, magnetic resonance imaging (MRI) can play an important role in evaluating UA and proper assessment of patients presenting with early-onset UA and, most importantly, provides a way to justify treatment with DMARDs in this domain. A highly sensitive and multiplanar technique such as MRI allows the detection of inflammatory and
destructive changes in inflammatory joint diseases, whereas
plain radiographs are almost normal in early cases with UA
shortly after disease onset. MRI can add much more
important information and can identify poor prognostic
signs such as early bony erosions, cartilaginous erosions, and
soft tissue edema (Figure 3).

Advances in MRI technology include contrast enhancement,
dynamic and quantitative, which allowed earlier initiation of
treatment with DMARDs [11]. Moreover, comparisons with
miniarthroscopy and histopathological findings have docu-
mented that MRI synovitis, as determined by contrast-
enhanced MRI, represents true synovial inflammation [12, 13].

In summary, MRI is a potentially important diagnostic tool
that can accurately quantify the degree of synovial inflamma-
tion in post-contrast MR images as well as detecting other
important prognostic signs non-invasively in early-onset UA,
and can be of help in early decision-making and justification
for treatment with DMARDs.

BONE MARROW EDEMA AS A PREDICTOR OF
BONE EROSIONS

Another important sign that cannot be visualized except with
the use of MRI is bone marrow edema (BME). BME is a general
term describing an area of low signal intensity on T1-weighted

Figure 3. (a) Sagittal STIR sequence showing Backer’s cyst (white arrow) and bone marrow edema of the femoral condyle (black arrow). (b) Sagittal STIR sequence showing periarticular soft tissue edema (white arrows). (c) Axial T2-weighted image showing denudation of the patellar articular cartilage (white arrow). (d) Sagittal STIR sequence demonstrating subcortical focal bony erosions (white arrow)
images, high signal intensity on T2-weighted images, and short T1 inversion-recovery sequence (STIR). BME as observed by MRI is neither a specific MRI finding nor a specific diagnosis, and can be observed in various forms of inflammatory and non-inflammatory arthritis [14]. BME as observed by MRI is relatively common in early and late RA and may be tied to the development of long-term joint damage. Before the advent of MRI, this process situated in the subchondral bone was unsuspected and certainly not in connection with any significance in terms of disease pathogenesis. Recently, BME in inflammatory arthritis has been shown to represent a cellular infiltrate within bone, and histopathological studies suggest that a cellular infiltrate composed of lymphocytes and osteoclasts may be detected in subchondral bone and could mediate the development of erosions from the marrow toward the joint surface. The implications are exciting and suggest a new focus for understanding disease pathology and influencing disease progression; moving away from the synovium and toward the bone marrow [15]. On the histopathological level, Gao et al [16] identified florid bone edema by MRI at the site of intended surgery in RA patients awaiting joint replacement or fusion, suggesting that BME may be especially associated with more destructive and aggressive disease. In another important and more recent work, Dalbeth et al [17] determined the cellular components of MRI bone edema, and clarified the relationship between bone erosion and MRI bone edema. The authors examined 28 bones from 11 patients with RA undergoing orthopedic surgery. Preoperative contrast-enhanced MRI scans were analyzed for bone edema, and bone specimens were analyzed by quantitative and semi-quantitative immunohistochemistry. The authors found that the density of osteoclasts was higher in those samples with MRI bone edema than in those without MRI bone edema ($p=0.01$). Other cells identified within bone marrow included macrophages and plasma cells, and these were more numerous in samples with MRI bone edema ($p=0.02$ and $p=0.05$ respectively). B cells were present in lower numbers, but B-cell aggregations were identified in some samples with MRI bone edema. Moreover, there was a trend to increased RANKL expression in samples with MRI bone edema ($p=0.09$). The latter correlated with the number of osteoclasts ($r=0.592$, $p=0.004$). In the authors’ opinion, the increased number of osteoclasts and RANKL expression in samples with MRI bone edema supports the hypothesis that bone erosion in RA occurs through activation of local bone resorption mechanisms within subchondral bone as well as through synovial invasion into bone.

BME as a predictor of bone erosions was explored by Haavardsholm et al [18], who evaluated 84 consecutive patients with RA with disease duration <1 year to examine the spectrum and severity of MRI findings in patients with early RA, and explored the predictive value of MRI findings for subsequent development of conventional radiographic (CR) damage and MRI erosions. In their study, MR images were scored according to the OMERACT rheumatoid arthritis magnetic resonance imaging score (RAMRIS), and conventional radiographs according to the van der Heijde modified Sharp score. The authors concluded that BME detected on MRI was an independent predictor of radiographic damage, and suggested that MRI scans of the dominant wrist may help clinicians to determine which patients need early and aggressive treatment to avoid subsequent joint damage. In more recent work, Hetland and collaborators [19] identified predictors of radiographic progression in a 2-year randomized, double-blind, clinical study (CIMESTRA) of patients with early RA. Baseline MRI of the wrist ($n=130$) or MRI of the wrist and metacarpophalangeal (MCP) joints ($n=89$) were assessed by OMERACT RAMRIS, and X-ray examination of hands, wrists, and forefeet by Sharp/van der Heijde score. In their study, baseline RAMRIS MRI bone edema scores of MCP and wrist joints were the strongest independent predictor of radiographic progression in hands, wrists, and forefeet after 2 years, whereas MRI synovitis score, MRI erosion score, DAS28, anti-CCP, SE, smoking, age, and gender were not independent risk factors.

A previous study has indicated that MRI synovitis, bone edema, and erosion can be detected within weeks of the onset of symptoms [20] and, in the previous studies, BME has repeatedly been shown to be the most important predictor of future erosions at the wrist [18, 19, 21]. Most important is the fact that MRI scans performed at the first presentation of RA can be used to help predict future radiographic damage, allowing disease-modifying therapy to be targeted to patients with aggressive disease [21].

Interestingly, in psoriatic arthritis (PsA), Tan et al [22] observed that MRI bone edema score was higher in PsA patients presenting the arthritis mutilans variety, and BME correlated strongly with erosion and joint space narrowing scores, suggesting that MRI bone edema could be a forerunner of articular damage in PsA and may be a useful biomarker to show aggressive disease. Given that the presence of BME in the affected joints of patients presenting with early UA has important therapeutic implications, this shows that aggressive disease onset with poor prognosis deserves the same attention.

The decision to start DMARDs in patients with recent-onset UA is complicated by a varied natural disease course in which the disease progresses to RA in one-third of patients, whereas 40–50% of patients experience spontaneous remission [23]. Several studies have shown a beneficial effect of the early treatment of RA to achieve a less severe disease course or even to induce remission. The possible extra therapeutic benefit attainable in this early period in the disease has been called the “window of opportunity” [24–26]. In terms of management, a watch-and-wait policy used to be common, attempting to avoid unnecessary toxicity from the use of DMARDs. However, by waiting for the classic features of the disease to emerge before starting therapy, effective intervention may be withheld, and an opportunity to improve the outcome may be missed. This approach differs markedly from the approach to the treatment of patients with newly diagnosed RA, in whom DMARD therapy would be started at the first visit. This lag time until treatment may represent reluctance of the clinician to start DMARDs in patients who lack recognizable disease patterns or the relatively mild nature of disease in most of these patients [27]. The EULAR expert panel formed a set of

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**MRI in undifferentiated arthritis**
recommendations based on a review of evidence-based literature, including early referral of patients with arthritis within 6 weeks, the use of MRI in the evaluation of such cases, and the early start of DMARD in patients at risk of developing persistent and/or erosive arthritis [28].

Moreover, enhanced MRI may play an important role in the evaluation of those patients presenting with early UA affecting the knee joint(s) and a way to justify prescribing DMARDs. Emad et al [29] showed that, after a short episode of conventional DMARD treatment, an improvement can be seen regarding synovitis and even bone marrow edema in a cohort of patients with early UA of the knee joints (Figure 4). In summary, achieving clinical and radiological remission is always a sought after goal in treating any form of arthritis, most notably RA, to prevent inevitable irreversible damage. Observing the clinical response to DMARDs as well as radiological remission using a sensitive technique such as MRI would be a very promising and interesting area of research among patients with UA.

CAN MRI DIFFERENTIATE UNDIFFERENTIATED ARTHRITIS?

The role of MRI in differentiating different forms of arthritis is still under discussion. MRI has been applied to define subsets of early synovitis patients on the basis of the distribution pattern of the inflammation. The data suggest two principal imaging patterns: one in which the inflammatory changes are based primarily in the synovium; and another in which the periarticular entheses are inflamed in association with intense edema of the adjacent bone. These two patterns are proposed to broadly classify patients with early synovitis into a “RA” phenotype where synovitis is the primary process, and a “spondyloarthropathy” (SpA) phenotype where enthesitis is the primary process and synovitis occurs on a secondary basis [30]. To date, most studies have examined MRI changes in the hand joints of patients with RA and seronegative SpA, most commonly PsA [30–34].

Jevtic et al [30] examined a series of patients with clinically early inflammatory joint disease resulting from RA, PsA, and Reiter’s syndrome by plain film radiography and MRI. The authors demonstrated distinct differences in the distribution of inflammatory changes, both within and adjacent to involved small hand joints. Two major subtypes of inflammatory arthritis were shown, thus providing a specific differential diagnosis between RA and some patients with seronegative spondyloarthritis. In particular, all the patients with Reiter’s syndrome who were studied, and half of those with PsA, had a distinctive pattern of extra-articular disease involvement. In a similar study, Marzo-Ortega et al [31] used dynamic contrast-enhanced MRI to examine 20 patients (10 each with early RA and PsA) who had swollen MCP joints. The authors aimed to determine whether MRI-related enthesal changes including osteitis and extracapsular edema could be used to differentiate between MCP joint involvement in RA and PsA. In their study, MRI was not able to differentiate at

![Figure 4](https://example.com/figure4.png)

Figure 4. (a) Sagittal STIR sequence showing moderate knee effusion. (b) Sagittal T1-weighted contrast-enhanced image with fat saturation before treatment showing villous synovial hypertrophy and enhancement. (c) Axial contrast-enhanced fat saturation weighted image showing subtle villous projections (before treatment with DMARDs). (d, e, and f) Corresponding MRI images after treatment with DMARDs showing appreciable regression of both effusion and synovitis.
the group level between both cohorts on the basis of enthesal-related disease, but a subgroup of PsA patients had diffuse extracapsular enhancement (30%) or diffuse bone edema (20%). The RA patient group had a greater degree of MCP synovitis (P<0.0001) and tenosynovitis than PsA patients (P<0.0001).

In terms of synovial enhancement, Cimmino et al [32] used dynamic MRI to examine 15 consecutive patients with PsA, 49 consecutive patients with RA, 30 RA patients matched for disease severity with those with PsA, and eight healthy control subjects. In their study, the enhancement ratio was calculated both as rate of early enhancement (REE), which shows the slope of the curve of contrast uptake per second during the first 55 s, and as relative enhancement (RE), which indicates the steady state of enhancement. The authors concluded that dynamic MRI cannot be used to differentiate PsA from RA. However, REE and RE were significantly higher in PsA than in normal control subjects, with only one instance of overlap between values found for the two groups.

In another study, Savnik and coworkers [33] used contrast-enhanced MRI to evaluate the wrist and MCP, proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints in four patient groups: (1) early RA (disease duration <3 years), n=28; (2) 25 RA patients with disease duration >3 years; (3) 25 patients with reactive arthritis, PsA, or mixed connective tissue disease; and (4) 25 patients with arthritis. In their study, MRI-determined BME and synovial membrane volumes provided additional information about disease activity, and may be used as a marker of it. Bone marrow edema appeared with the highest percentage in patients with long duration of RA (>3 years) and is probably secondary to changes in inflammatory activity. In similar work, Schoellnast et al [34] compared contrast-enhanced MRI findings of the wrist and the hand joint in 18 patients with PsA and 21 RA patients. In their study, MR images were evaluated for periarticular soft tissue swelling, synovitis, effusion, periostitis, bone edema, bone erosions, bone cysts, and tenosynovitis. The authors found that erosions were statistically more frequent in patients with RA (P<0.05), whereas periostitis was significantly higher in patients with PsA (P<0.05), and no significant difference was found in the frequency of synovitis, BME, bone cysts, and tenosynovitis between the two groups. Moreover, the radiocarpal joint, the midcarpal joints, the carpometacarpal joints, and the metacarpophalangeal joints were significantly more affected in patients with RA compared with PsA patients (P<0.05), whereas the proximal interphalangeal joints were significantly more frequently affected in patients with PsA (P<0.05).

CAN MRI DIFFERENTIATE UNDIFFERENTIATED ARTHRITIS BASED ON KNEE IMAGING?

McGonagle and colleagues [35] were the first to describe characteristic MRI enthesal changes involving the knee joints in a cohort of 10 patients with SpA (three of whom had PsA) with knee swelling of recent onset. They observed an increased signal on T2-weighted images, characterizing “focal extracapsular fluid/edema” in enthesal portions of the patellar tendon, the iliitibial band, and adjacent to the posterior capsule of the knee. Periarticular BME was present in six SpA patients, including one with PsA, in whom it involved bone at the tibial plateau as well as bony attachments of the patellar tendon and posterior cruciate ligament. These findings suggest that knee synovitis in patients with early PsA and SpA-associated monarthritis/oligoarthritis is often characterized by clinically unrecognized enthesitis near the swollen joint, which suggests that enthesitis may be the primary lesion. This is supported by the observation that enthesopathic inflammation may extend as far as the synovial cavity.

Inflammation at the entheses, the sites of attachment of tendon, ligament, fascia, or joint capsule to bone, is a distinguishing pathological feature of the spondyloarthropathies (SpA) including PsA [36]. Oriente et al [37] have found peripheral enthesitis in 20% of their patients with PsA, with a peak value of 30% in the spondylitic pattern, and a subset of PsA patients may present with isolated enthesitis and/or dactylitis. Peripheral PsA synovitis appears similar to RA synovitis on static and dynamic MRI; however, bone erosions in PsA do not have disease-specific MRI features, and little is known concerning how they progress over time. With enthesitis, dactylitis, and spondylitis, the MRI features of PsA depart from those of RA and conform to the SpA group of disorders [38].

McGonagle and associates [35], using fat-suppressed MRI, evaluated enthesal-related changes involving the knee joint in patients with RA (n=10) and SpA (n=10) to determine whether the primary site of abnormality differs. The authors observed that all 10 SpA patients, but only four of the 10 RA patients, had focal perienthesal high signal (compatible with fluid or edema) outside the joint (P=0.01). In their study, six of the SpA patients had BME that was maximal at entheselial insertions; in four cases, this was multifocal, and none of the RA patients showed such an abnormality (P=0.01). The authors concluded that prominent enthesal abnormalities on MRI are a consistent feature of new-onset synovitis in SpA, but are a minor feature of RA [1]. In their study, two significant findings were reported: first, focal soft tissue edema outside the joint capsule adjacent to enthesal insertions (perienthesal fluid/edema) was common, and this is probably secondary to enthesitis, whereas the soft tissue abnormalities outside the joint that were seen in a subset of RA patients may be secondary to severe synovitis with non-specific extension of the inflammatory process beyond the joint capsule. Second, BME that was maximal adjacent to enthesal insertions was seen only in SpA, and was accompanied by perienthesal fluid or edema. This pattern of bone edema seen in their study has been reported previously in relation to peripheral enthesitis and spondylitis, which suggests a common pathogenic link between spinal disease, peripheral enthesitis, and knee synovitis in SpA. The same group also studied calcaneal enthesopathy in 17 early SpA patients (including four with PsA), and similar findings were described, again often including underlying BME [39].

In a more recent work, Emad et al [5] compared enhanced MRI of the knee joints in oligoarticular UA in those with
established RA and SpA. The authors evaluated a total of 55 consecutive patients with knee arthritis: 25 with undifferentiated oligoarthritis of the knee joint(s), 15 RA patients, and another 15 patients with SpA. In terms of enthesitis, MRI examination showed enthesitis in all patients in the SpA group at different anatomical locations: fibular collateral ligament in one patient (6.7%), fibular insertion of biceps femoris in two (13.3%), posterior cruciate ligament (PCL) in four (26.7%) (Figure 5a–c), medial collateral ligament (MCL) in seven (46.7%), and patellar tendon in five (33.3%). Moreover, three patients (12%) in the UA group showed enthesitis of MCL (Figure 5d), whereas none of the patients in the RA group showed such an abnormality ($P=0.01$).

Entheseal-related changes in the knee joint observed by MRI in a group of SpA patients are unique and provocative findings and may be an early (perhaps the earliest) sign of inflammation. In our opinion, utilizing these currently available data reviewed previously can be important in the initial evaluation of undifferentiated oligoarthritis of the knee joint(s) for diagnostic and classification purposes, and can also be useful in determining the evolving pattern in these domains. Distinguishing features on MRI may help to differentiate an undifferentiated inflammatory arthritis depending on the pattern of inflammation and structures involved. MRI of a symptomatic knee may help to make a more definitive diagnosis as a large percentage of patients with SpA have enthesitis on MRI, and no patients with RA have enthesitis in the studies reviewed.

Future research should focus on enthesal-related changes shown by MRI of the knee joint and include a larger number of patients in all diseases representative of SpA, including PsA, ankylosing spondylitis, reactive arthritis, ulcerative colitis, Crohn’s disease, and even those patients with skin psoriasis only without clinically evident synovitis, to examine the frequency of such changes in this domain.

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