Concepts in diagnosing, scoring, and monitoring tenosynovitis and other tendon abnormalities in patients with rheumatoid arthritis – the role of musculoskeletal ultrasound.

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Abstract

In the last years, important advancements have been made in implementing high resolution imaging related information inside the global management algorithm in RA patients. Musculoskeletal ultrasound has already proven its utility in visualizing directly the joint synovial tissue, the synovial vascularization and in monitoring the response to therapy. Recently, much attention has been given to the presence of tenosynovitis, as a constant, complementary but different facet of the inflammatory involvement in RA. Tenosynovitis identification in early RA stages may allow adequate treatment adjustment in early and established disease in order to prevent and/or slow down the development of structural damage at tendon and joint level.

Keywords: tenosynovitis, ultrasound, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) management should focus on inflammation suppression, therefore, limiting as much as possible the disease damage progression at joint and peri-articular level. Achievement and maintenance of a good quality of life during the disease course is tightly linked to an early, accurate diagnosis and to a tailored treatment commencement and adjustment, aiming at sustained remission [1-4]. In this regard, it is of the utmost importance to perform an accurate baseline disease activity and follow-up outcome assessment [5].

However, the presence of subclinical residual inflammatory joint activity with subsequent documented radiological progression in more than 25% of patients attaining clinical remission, has triggered attention for complementary evaluation methods [6-17].

Lately, important advancements have been made in implementing high resolution imaging related information inside the global management algorithm in RA patients [6-9]. Currently, available evidence supports the important contribution of several high resolution imaging methods in identifying joint, peri-articular, and erosive changes at any point during the disease course. Musculoskeletal ultrasound (MSUS) has already proven its utility for directly visualization of the joint synovial tissue (morphology and quantification), the synovial vascularization (presence and quantification), and in monitoring the response to therapy [18-27]. Recently, much attention has been given to the presence of tenosynovitis, as a constant, complementary, but different facet of the inflammatory involvement in RA [28-30]. In this scenario, identification of tenosynovitis in early RA stages along with treatment monitoring in early and established disease should not only help in improving the new classification criteria but also in preventing or slowing down the development of structural damage at tendon and joint level [31-34].

Clinical and imaging evaluation

The first descriptions regarding the presence of tenosynovitis as a clinical finding in early RA (ERA) are
present in the literature since 1957. Jacobs et al reported three cases of patients with RA onset where tenosynovitis was the primary manifestation. The authors underlined the fact that tenosynovitis may occur as isolated attacks at the disease onset and should not be overlooked [35]. In fact, tenosynovitis is frequently overlooked in clinical practice because clinical examination (CE) might be very challenging in patients with multiple inflammatory and structural joint and peri-articular pathology, occurring in complex anatomical areas such as the hand or foot. Indeed, conventional radiology does not offer satisfactory information about the soft tissues. Therefore, high resolution imaging methods such as magnetic resonance imaging (MRI) and MSUS are extremely useful since clinical and subclinical joint and peri-articular involvement is accurately detected [29-32].

The new ACR/ EULAR classification criteria for RA were developed in order to identify individuals at high risk of persistent and destructive disease, who might benefit from disease-modifying therapy. However, these criteria are not perfect since only the presence of synovitis, erosions and laboratory parameters are included.

Cader et al highlighted in a paper published in 2011 that the new ACR/ EULAR classification criteria for RA may still lead to significant over – and under – diagnosis within the first months after symptom onset and may overlook patients with symmetrical seronegative arthritis and limited joint involvement. Therefore, identification of additional, more sensitive and specific tests/ imaging information for very early detection of RA is needed in the field of rheumatology [36].

However, the EULAR recommendations for the use of imaging of the joints in the clinical management of RA are focusing strictly on the early articular evaluation using MRI or MSUS without taking into consideration a possible peri-articular involvement [9]. On the other hand, the ACR report on reasonable use of MSUS in rheumatology clinical practice mention the fact that “For a patient with peri-articular pain without definitive diagnosis on clinical examination, it is reasonable to use MSUS to evaluate tendon and soft tissue pathologies and the nature and localization of adjacent swelling at the shoulder, elbow, hand, hip, knee, ankle, and forefoot” [7].

In the last 10 years, several papers have drawn attention to tenosynovitis as a phenomenon present from the early stages of the disease, evolving in parallel with joint inflammation. Mc Queen et al report tenosynovitis in the dominant wrist, especially in the first year of disease, to be a frequent finding found at MRI examinations [37]. Indeed, another MRI based longitudinal study conducted by Lindegaard et al concluded that tenosynovitis in the dominant wrist and at MCF level was present in about 60% of the ERA patients at baseline with reduction to 28% after 6 months and a yearfollow-up, showing a good response to therapy superior to the synovitis response [38].

Wakefield et al reinforced the idea in a paper published in 2007, a paper in which the frequency and distribution of finger tenosynovitis in non-treated ERA patients was studied using two imaging methods: MSUS and MRI. The authors identified 28%/ 64% flexor tenosynovitis and 14%/ 40% extensors tenosynovitis on MSUS vs MRI. No controls showed imaging tenosynovitis [29]. In patients with undifferentiated arthritis or patients with clinically suspected RA at the time of presentation, who had no typical findings of RA on conventional radiographs, Esched et al found a statistic significant difference when analyzing tenosynovitis between RA and non-RA patients. The ratio flexor/ extensor tenosynovitis was 60%/ 14% in RA patients compared to only 24% / 12% in non-RA patients, pointing out the importance of tenosynovitis of the flexor tendons for the early stages of the disease for the diagnostic of RA. This parameter was the strongest early predictor of RA compared to other imaging parameters. When ACR criteria were added to the logistic regression analysis, only the presence of the rheumatoid factor (RF) was stronger than tenosynovitis of the flexor tendons for the prediction of RA [39].

Furthermore, other recent studies evaluated the presence of wrist tenosynovitis (especially of the extensor carpi ulnaris and flexor tendons) in early and very early disease stages (VERA) and showed that its presence was most significantly associated with progression to RA. Tenosynovitis was proved to be an additional parameter that should be separately monitored. Its presence is linked to the improvement of the diagnostic capacity (sensitivity) of the new classification criteria [31,32,40]. Of note, Navalho et al identified MRI tenosynovitis as a discriminating factor of the evolution toward RA in patients with VERA (onset <3 months). Extensor carpi ulnaris (EUC) and flexors of the second finger tenosynovitis in addition to radio-carpal joint synovitis were recognized as significantly associated with progression to RA. Tenosynovitis of the flexor tendons of the second finger remained a discriminating feature even in patients with longer disease duration [32].

MSUS is a very useful imaging tool for baseline assessment and further monitoring since it is non-radiating and more sensitive in detecting clinical and subclinical synovitis and tenosynovitis in comparison to CE in RA target areas [30,40-44]. Moreover, MSUS has been considered by some authors as the “goldstandard” method for the evaluation of superficial tendons [45]. In comparison to MRI it permits not only multi-planar evaluation but also real time dynamic assessment and vasculariza-
tion detection [42,46-54]. MSUS evaluation can be repeated anytime during the disease course, offering a key to a better understanding and monitoring in early stages and longstanding disease. In fact, MSUS creates the possibility to analyze better the transition between inflammatory tendon pathology to partial or total damage.

**OMERACT filter – validity, reliability, responsiveness and feasibility. Scoring systems.**

A lot of effort has been made in the last years to develop a common language between different evaluators and centers. This process requires the elaboration of better US definitions, a better image acquisition standardization and the improvement of the inter-observer reliability parameters for inflammatory as well as for tendon damage lesions. The final goal would be to implement the tendons MSUS evaluation in clinical practice as well as in clinical trials.

The Outcome Measures in Rheumatology (OMERACT) Ultrasound group published definitions for tenosynovitis and tendon damage and proposed recently a tenosynovitis US scoring system [34,55-60].

Tenosynovitis was initially defined as hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in 2 perpendicular planes and which may exhibit a Doppler signal [55]. This definition has suffered some adjustments over time and remarks regarding the Doppler signal extension and differentiation from normal feeding vessels and also has included the definition of a normal tendon (Table I) [57].

Tendon damage was defined as an internal and/or peripheral focal tendon defect (ie, absence of fibres) in the region enclosed by the tendon sheath, seen in two perpendicular planes [34].

A number of important studies dealt with construct validity where MSUS had different comparators such as CE, MRI, X-ray, or laboratory data. The presence of tenosynovitis was in generally correlated with the CE and inflammatory laboratory parameter. MSUS assessment detected more tendon pathology in comparison to clinical evaluation but was less sensitive in comparison to MRI. Overall, MSUS showed a fair to moderate sensitivity but a high specificity [28,29,31,33,37,46,60-72].

Regarding criterion validity, Swen et al studied concurrent validity of US in the detection of tendon tear in RA patients who were exposed to hand surgery due to the persistent tenosynovitis [63]. In a recent study, Janta et al used a surrogate model (cadaver), with previously prepared tendon damage, testing the MSUS detection of the tendon pathology in an inter-observer exercise [73].

The predictive validity of US tenosynovitis in relation to radiographic progression was reported by the group of Lillegraven S et al [74]. The study has demonstrated that MSUS-assessed tenosynovitis (ECU) predicts the development of erosive joint damage in a cohort of early RA patients [74].

Previously, the same group reported a predictive value of an overall ultrasonography score and a cross-sectional association between MSUS erosions and erosions assessed by MRI and conventional radiographs [75]. The predictive value of MSUS in detecting the RA patients in unstable remission was reported recently by Janta et al in a study comparing different reduced joint MSUS assessment of synovitis and tenosynovitis. No estimation regarding the impact of MSUS PD tenosynovitis could have been made in this group of patients since no patient in clinical remission presented PD tenosynovitis [76]. Similar results were found by Vlad et al in a recent study evaluating MSUS synovitis and tenosynovitis response to biologic therapy [77]. Both studies suggest that MSUS-assessed tenosynovitis may be closer to clinically assessed remission than MSUS-assessed synovitis in patients with RA.

Reliability for tendon abnormalities assessment was published in several recent studies focusing on inter-observer/ intra-observer reliability, inter-observer acquisition and inter- intra-observer reading reliability [56,59,73,78].

**Tenosynovitis and other tendon abnormalities scoring systems**

A variety of scoring systems were developed in time for the tenosynovitis assessment – binary scoring sys-

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<tr>
<td>Tendon</td>
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<td>Hyperechoic (relative to subdermal fat) fibrillar pattern (ie, hyperechoic parallel lines in longitudinal planes and hyperechoic dots in transverse planes).</td>
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<tr>
<td>Tendon synovial sheath</td>
</tr>
<tr>
<td>A thin regular hypoechoic (relative to tendon fibres) halo surrounding/ thin regular hypoechoic lines above and below the tendon structure in transverse/longitudinal plane respectively at anatomical sites where synovial sheaths are known to exist and which can be distinguished from pulleys and retinaculae.</td>
</tr>
<tr>
<td>Retinaculae and pulleys</td>
</tr>
<tr>
<td>Focal hypoechoic (relative to tendon fibres) thickening of the peritendinous tendon sheath with fibrillar pattern in the area located perpendicular to the probe, at its expected normal anatomical location.</td>
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tems, semi-quantitative grey scale or combined grey scale and Doppler and global inflammatory scores (synovitis and tenosynovitis) [25,26,65,69,77,79-83]. Recently, OMERACT proposed a new four-grade tenosynovitis scoring system along with a more detailed definition of the normal tendons and related structures, description of the elementary lesions of tenosynovitis on B-mode and Doppler mode and definition of tenosynovitis (table II, table III) [57]. This scoring system quantifies the Doppler signals within the widened synovial sheath and inside the tendon belly, excluding those in characteristic locations of the feeding blood supply.

Multicentric inter-observer reliability proved to be good for power Doppler (PD) evaluation, moderate for B-mode assessment. Intra-observer agreement was good for B-mode as well as for PD assessment [84].

For the tendon damage a recent scoring system was elaborated by Bruyn et al [85]. The expert panel underlined the necessity to assess the tendon damage in both planes: transversal and longitudinal. They established a four-grade semi-quantitative scoring system (ie, grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe) in order to score the tendon damage using B mode US. Among experienced ultrasonographers, inter-observer and intra-observer reliability was high, showing relevance for clinical practice [85].

Responsiveness and feasibility of MSUS detected tenosynovitis.

So far, MSUS detected tenosynovitis proved to be responsive to effective treatment in RA patients. Sensitivity to change was studied in a number of recent studies [25,75,79-82,86,87]. Feasibility of the method was tested in several papers [25,28, 59,80]. Naredo et al performed an intra and inter-observer exercise with 35 examiners and concluded that intra-observer reliability for both GS and PD assessment was good (k values 0.72 vs 0.78) and that inter-observer reliability was moderate for GS (k=0.47) and good for PD assessment (k=0.60) concluding that MSUS is a reproducible tool useful for the evaluation and monitoring tenosynovitis [25]. Boyesen et al demonstrated in a study performed on 53 patients that both high resolution imaging methods (MSUS and MRI) are independent predictors for further bone erosion development and that both methods were superior to other predictor parameters such as anti CCP antibodies, RF and DAS 28. MSUS for GS evaluation performed best [75]. Naredo et al performed a multicentric Spanish study on 279 patients evaluating PD articular and peri-articular activity testing the validity, responsiveness and predictive value of PDUS in monitoring response to TNF alpha blocking agents in RA. A significant parallel decrease of

Table II. Ultrasoundographic definitions of tendon sheath abnormalities – adapted from [57].

<table>
<thead>
<tr>
<th>Definition</th>
<th>Tenosynovitis, B-mode</th>
<th>Tenosynovitis, Doppler mode</th>
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<tr>
<td>Abnormal anechoic and/or hypoechoic (relative to tendon fibres) tendon sheath widening which can be related to both the presence of tenosynovial abnormal fluid and/or hypertrophy</td>
<td>Tenosynovitis, B-mode</td>
<td>Peritendinous Doppler signal within the synovial sheath, seen in two perpendicular planes, excluding normal feeding vessels (ie, vessels at the mesotenon or vinculae or vessels entering the synovial sheath from surrounding tissues) only if the tendon shows peritendinous synovial sheath widening on B-mode.</td>
</tr>
<tr>
<td>Presence of abnormal anechoic or hypoechoic (relative to tendon fibres) material within the synovial sheath, either localised (eg, in the synovial sheath cul-de-sacs) or surrounding the tendon that is displaceable and seen in two perpendicular planes.</td>
<td>Tendon sheath effusion</td>
<td>Presence of abnormal hypoechoic (relative to tendon fibres) within the synovial sheath that is not displaceable and poorly compressible and seen in two perpendicular planes.</td>
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Table III. US scoring system for tenosynovitis on B-mode and Doppler mode- adapted from [57].

<table>
<thead>
<tr>
<th>Grade</th>
<th>B mode</th>
<th>Doppler mode</th>
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<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>No Doppler signal</td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
<td>Minimal: peritendinous focal signal within the widened synovial sheath (ie, signals in only one area of the widened sheath), seen in two perpendicular planes, excluding normal feeding vessels</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Moderate peritendinous multifocal signal within the widened synovial sheath (ie, signals in more than one area of the widened sheath), seen in two perpendicular planes, excluding normal feeding vessels</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Severe, peritendinous diffuse signal within the widened synovial sheath (ie, signals filling most of the widened sheath), in two perpendicular planes, excluding normal feeding vessels</td>
</tr>
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If in addition to an abnormal intra-sheath signal there was an abnormal intratendinous signal seen in two perpendicular planes, then grades 1 and 2 would be increased by one point.
all clinical, functional and PDUS parameters was found at follow-ups. The authors found a high degree of intra
and inter-observer reliability and a statistic significant
sensitivity to change for PD assessment [80]. The same
results regarding the sensitivity to change were obtained
by Hammer et al in a study recruiting 20 patients when
calculating the dynamic change of the sum scores in ex-
tensor carpi ulnaris and tibialis posterior tendons in pa-
tients with RA [81].

Backhaus et all evaluated in 120 patients the semi-
quantitative findings of PDUS activity (synovitis and ten-
osynovitis) and found a good inter and intra-reader agree-
ment for both GS and PD assessment (k values 0.62 vs
0.84; k values 0.83 vs 0.64). For tenosynovitis, a 64.3%
inter-reader agreement was found [82]. The same results
were obtained by Bruyn et al in an exercise evaluating 9
patients (13 experts). An intra-observer agreement was
0.55 for GS inflammatory lesion detection versus 0.64
for PD evaluation. For tendon damage the intra-observer
agreement k was 0.66 for PD and 0.53 for GS evalua-
tion. Inter-observer evaluation showed substantial over-
all agreement 80-89% for GS assessment and 97-100%
for PD assessment in both inflammatory and structural
lesions detection [59].

Conclusions

MSUS is a promising imaging tool complementary
to CE for evaluating and monitoring tendon abnor-
malities. The easy access to the ultrasound and the possibility
to perform quickly, multiple anatomic areas assessment,
and to repeat this assessment at any point during the dis-
ease course without exposing the patient to radiation or
any other danger, represents the key to a successful “treat
to target “ strategy and to a better functional outcome.

Conflict of interest: none

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