Musculoskeletal ultrasound scoring systems: assessing disease activity and therapeutic response in rheumatoid arthritis

Several musculoskeletal ultrasound scoring methods exist to monitor rheumatoid arthritis disease activity and the therapeutic response to immunosuppressive therapies. Qualitative (0/1) and different semiquantitative (0–3) systems as well as quantitative measurements are used. The semiquantitative 4-grade system developed by Szkudlarek *et al.*, which evaluates joint effusion, synovial thickening, bone erosion and power Doppler activity, is mostly applied. Thus far, an internationally accepted US sum scoring system does not exist. The novel seven-joint ultrasound (US7) score is the first US composite scoring system that combines soft tissue lesions (synovitis and tenosynovitis/paratenonitis) and destructive processes (erosions) in a single scoring system. By that, the implementation of the US7 score can quickly and easily give an overview of current disease activity in daily rheumatologic practice. Furthermore, its use in therapy monitoring is very helpful. This article reviews the development of different US scores and sum-scoring systems in a chronological order and contains current and future activities in this field.

KEYWORDS: erosion ▪ musculoskeletal ultrasound ▪ rheumatoid arthritis ▪ scoring system ▪ synovitis

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Imaging scoring systems are developed in order to standardize and objectify clinical findings. In rheumatology, scoring systems are used to monitor disease activity and therapeutic response with the consequence of adapting immunosuppressive therapy. With the rapidly growing number of disease-modifying drugs, especially with the use of biologics for the treatment of rheumatoid arthritis (RA), a new era has started with clinical remission as the most important aim ('treat to target') [1]. Several studies have already demonstrated that biologic therapies not only lead to significant improvements in clinical status but also to significant inhibition of radiographic progression [2–6], but these new therapies are of high cost. Consequently, a reliable method is required to objectify the therapeutic effectiveness. In monitoring RA different clinical scores (i.e., DAS28) exist which reflect the clinical disease activity and therapeutic response in a standardized manner. However, clinical scores are limited owing to the fact that in spite of clinical remission, radiographic progression is possible, and the erosive process predicts the outcome of the disease [7]. Therefore, objective imaging modalities are necessary to detect the destructive process as early as possible. The inflammatory soft tissue and erosive bone process in RA can be detected early and sensitively by musculoskeletal ultrasound (US) [8–12]. Accurate assessment of disease activity and joint damage in RA is important and standardization is therefore essential. During the 7th Outcome Measurement in Rheumatology Clinical Trials (OMERACT) conference, the typical RA findings detected by US including effusion, synovial hypertrophy/proliferation, tenosynovitis and erosion were defined [13]. In the scoring of US findings, quantitative measurements and semiquantitative systems can be differentiated. The grade of the synovial/tenosynovial and erosive process can therefore be estimated. Besides, US findings can easily be described on a qualitative (yes/no) basis. Unfortunately, to date, an international available and accepted musculoskeletal US (composite) scoring system does not exist.

Musculoskeletal US: equipment & findings

In general, musculoskeletal US is performed by linear transducers. The frequency of the sound waves sent by US transducers determines the penetration into tissue. For the best resolution in small joints such as wrist, finger and toe joints, high-frequency transducers of 10–20 MHz are recommended. The middle-size joints are examined by 10–12-MHz transducers and the big-size and deeply lying joints such as the hip are scanned by 5–7.5-MHz transducers. For each joint region standardized multiplanar scans exist according to the guidelines of the German Society for Ultrasound in Medicine (DEGUM) [14] and the guidelines of the European League against Rheumatism (EULAR) [15]. By applying them, a complete joint scanning is guaranteed. In

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addition, a dynamic examination is necessary in order to detect small fluid collections. The supplemental use of power Doppler (PD) US helps in differentiating active from inactive synovial/tenosynovial processes, especially in small joints.

The inflammatory joint process includes effusion and/or synovial hypertrophy/proliferation and is defined by the OMERACT as follows [13]:

- effusion: abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible, but does not exhibit Doppler signal;
- synovial hypertrophy/proliferation: abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal.

The inflammatory periarticular process includes tenosynovitis, which is defined by the OMERACT as follows:

- tenosynovitis: hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath with possible signs of Doppler signals, which is seen in two perpendicular planes.

The bone process in RA is characterized by erosions defined by the OMERACT as follows:

- RA bone erosion: an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes.

Development of different US scoring systems: chronological order

In recent years, different US scoring systems have been proposed. For a detailed chronological overview of the existing US scoring systems see Table 1.

Wakefield *et al.* first proposed a semiquantitative scale for the measurement of erosions as follows: small erosion: less than 2 mm; moderate

Table 1. Ultrasound scoring systems.

Author (year)	Pathologies	Grade	Examined joints	Joint region	Patients (n)	Abbreviation/ acronym of the sum score (if available)	Ref.
Wakefield *et al.* (2000)	Bone erosion	0–3	Unilateral MCP II–V	Ulnar, radial, palmar, dorsal	100	NA	[12]
Stone *et al.* (2001)	PD activity	0–3	MCP joints	Dorsal	12	NA	[17]
Szkudlarek *et al.* (2003)	Joint effusion Synovial thickening Bone erosion PD activity	0–3	Unilateral MCP II, III, PIP II, MTP I, II	Dorsal	30	NA	[18]
Scheel *et al.* (2005)	Synovitis	0–3	Unilateral MCP II–V, PIP II–V	Palmar, dorsal	46	NA	[19]
Naredo *et al.* (2005)	Joint effusion Synovial thickening PD activity	0–3	Sum of bilateral 60-, 18-, 16-, 12-, 10-, 6-joint score	Dorsal	49	NA	[20]
Loeuille *et al.* (2006)	Synovitis Tenosynovitis PD activity	0–3	Unilateral wrist, MCP II, III, V, MTP II, III, V	Dorsal (synovitis), palmar (tenosynovitis)	16	ScUSI	[21]
Chary-Valckenaere *et al.* (2006)	Bone erosion Joint-space narrowing	0–3	Bilateral MCP II, III, V, MTP II, III, V	Dorsal, lateral (MCP II, V, MTP V)	62	ScUSST	[23]
Backhaus *et al.* (2009)	Synovitis Tenosynovitis/ paratenonitis PD activity Bone erosions	0–3; 0/1 for tenosynovitis and erosion	Unilateral wrist, MCP II, III, PIP II, III, MTP II, V	Dorsal, palmar, lateral	120	US7	[25]
Dougados *et al.* (2010)	Synovitis PD activity	0–3; 0/1	Bilateral 28 joints vs 38 joints (28 + MTPs) vs 20 joints (20 MCPs + 20 MTPs)	Dorsal	76	NA	[28]

MCP: Metacarpophalangeal; MTP: Metatarsophalangeal; NA: Not available; PD: Power Doppler; PIP: Proximal interphalangeal; ScUSI: Scoring by UltraSound Inflammation; ScUSST: Scoring by UltraSound Structural Total; US7: Seven-joint ultrasound.

erosion: 2–4 mm; and large erosion: larger than 4 mm. In the study, the metacarpophalangeal (MCP) joints II–V of the clinically dominant hands of 100 RA patients were scanned from ulnar, radial, palmar and dorsal for erosions, of which the most (73%) were found either from radial or ulnar. Here, the interobserver κ value between two observers was at least 0.76 for present/absent erosions [12].

Szkudlarek *et al.* compared PD US, which was only scored as present or absent in this study, for the assessment of inflammatory activity in MCP joints of RA patients and found it reliable using dynamic MRI as the reference method [16].

At that time, Stone *et al.* introduced a semiquantitative score for PD US in affected MCP joints by RA. In this study, 12 RA patients were enrolled and synovial blood flow in a maximum of five MCP joints per patient was examined by PD as follows: grade 0: no color pixel; grade 1: less than one-third; grade 2: one-third to two-thirds; and grade 3: more than two-thirds is/are filled with color pixel [17]. Patients were examined before and after treatment with steroids and a significant change ($p < 0.002$) of PD signal was detected.

Shortly after, Szkudlarek *et al.* introduced a 4-grade semiquantitative US scoring system evaluating joint effusion, synovial thickening, bone erosion and PD activity on a larger scale. In the study, five preselected small joints of 30 RA patients (unilateral MCP II, III, proximal interphalangeal [PIP] II, and metatarsophalangeal [MTP] I, II joints examined from dorsal) were examined. Joint effusion was defined as a compressible anechoic intracapsular area and semiquantitatively examined as follows: grade 0: no effusion; grade 1: minimal amount; grade 2: moderate (without distension of the joint capsule); and grade 3: extensive (with distension of the joint capsule) amount of fluid. Synovial thickening was defined as a noncompressible hypoechoic intracapsular area examined as follows: grade 0: no synovial thickening; grade 1: minimal synovial thickening; grade 2: synovial thickening bulging over the line linking tops of the periarticular bones without extension along the bone diaphyses; and grade 3: synovial thickening bulging over the line linking tops of the periarticular bones with extension to at least one of the bone diaphyses. Bone erosions were defined as follows: grade 0: normal bone surface; grade 1: bone surface irregularity without seeing the defect in two planes; grade 2: defect of the surface in two planes; and grade 3: bone defect creating extensive bone destruction. The definition for the semiquantitative grading of the PD evaluation differed from the one that was described by Stone *et al.* and was defined as follows: grade 0: no flow; grade 1: single vessel signals; grade 2: less than half of the area of the synovium is filled with vessel signal; and grade 3: more than half of the area of the synovium is filled with vessels (FIGURE 1). This group proved the reproducibility of this scoring system by evaluating the interobserver agreement of two investigators with different backgrounds (rheumatologist vs radiologist). They found fair-to-good interobserver agreement rates (κ values from 0.48 to 0.68) for the identification of synovial abnormality and bone erosions using this newly introduced semiquantitative scoring system, concluding that US is a reproducible method in the examination of finger and toe joints of RA patients [18]. In the study by Szkudlarek *et al.* sum scores were not performed.

On developing a novel synovitis sum scoring system for the evaluation of finger joint inflammation of RA patients, Scheel *et al.* assessed clinically dominant MCP II–V and PIP II–V joints from dorsal and palmar and examined each joint region semiquantitatively (0–3) and quantitatively (mm). In this study, synovial hypertrophy and synovial fluid were, in contrast to the study by Szkudlarek *et al.*, combined in the term 'synovitis'. The semiquantitative synovitis assessment was performed as follows: 0: absence; 1: minimal effusion/hypertrophy (little synovitis); 2: moderate effusion/hypertrophy (moderate synovitis); and 3: extensive effusion/hypertrophy (high synovitis). This group found that synovitis was more frequently detected in the palmar proximal area (86% of the affected joints) of the MCP and PIP joints than from the dorsal side. Furthermore they could demonstrate that there was no significant difference between semiquantitative scores and quantitative measurements. In this study, the best results for combined joint counts were achieved using the sum score of four fingers (s4) including the joints MCP II–V and PIP II–V, and the sum score of three fingers (s3) including the joints MCP II–IV and PIP II–IV (each area under curve [AUC] of 0.9). Nonetheless, there were similarly good results for the sum score of two fingers (s2) including MCP II–III and PIP II–III (AUC 0.85), with the consequence that a reduced number of examined joints is preferable, especially in terms of examination time [19].

Naredo *et al.* also investigated the validity of reduced joint counts. This group found that a 12-joint score (bilateral wrist, MCP II, III,

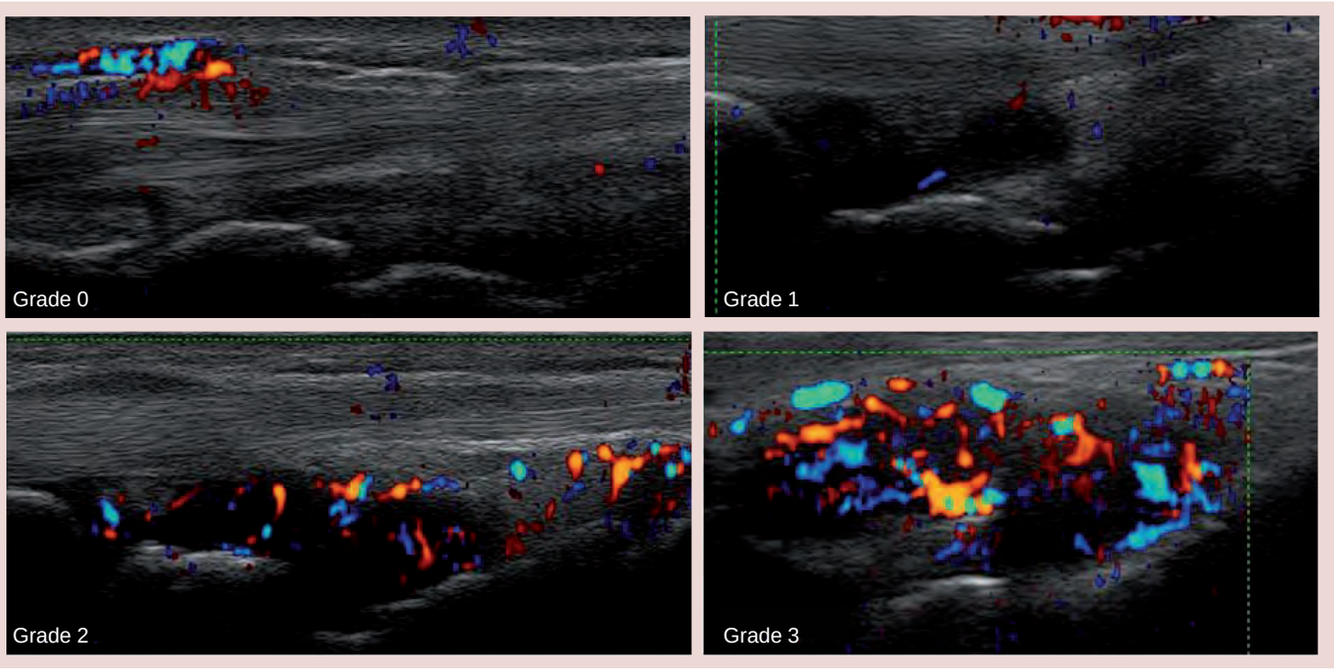

Figure 1. Synovitis in the dorsomedian wrist region by power Doppler mode.

PIP II, III and the knee) detecting effusion, synovial hypertrophy/proliferation and PD signal highly correlated with a corresponding 60-joint score. They concluded that a 12-joint score effectively reflects overall joint inflammation in RA patients and might, therefore, be a useful tool [20].

The novel semiquantitative US score Scoring by US Inflammation (ScUSI), introduced by Loeuille *et al.,* is the sum of the grades of synovial inflammation from dorsal and tenosynovitis from palmar on grayscale US mode according to Szkudlarek [18] multiplied by their respective grade on PD images. ScUSI includes the US examination of seven joints (wrist, MCP II, III, V, MTP II, III, V). This group demonstrated that ScUSI was a better predictive factor of radiographic progression after 7 months of follow-up than the clinical score DAS28, concluding that US might be used in addition to clinical assessment [21]. Loeuille *et al.* further presented that a mean number of PD positive joints greater than four or a mean ScUSI higher than 16 may be considered as the US inflammatory thresholds for RA disease activity requiring treatment readjustment [22]. Chary-Valckenaere *et al.* developed an US sum score for structural lesions, such as erosions and joint space narrowing, called Scoring by US Structural Total (ScUSST). In this score dorsal and palmar or plantar bone surfaces of 12 preselected joints – bilateral MCP joints II, III, V and MTP joints II, III, V as well as the lateral sides of bilateral MCP II, V and MTP V joints – were examined by grayscale US mode. Erosions were scored semiquantitatively as follows: grade 0: absence of erosion; grade 1: small erosion smaller than 2 mm; grade 2: erosions of 2–3 mm or larger, or two erosions smaller than 2 mm; and grade 3: erosion larger than 3 mm or multiple erosions. The joint space narrowing was semiquantitatively graded after the following criteria: grade 0: normal joint; grade 1: irregular aspect of cartilage; grade 2: loss of cartilage; grade 3: destruction or luxation of joint. This group found out that ScUSST correlated well with the radiographic Sharp score, especially in patients with a disease duration longer than 2 years. In this study, the most altered joints were MTP V, then MCP II and MCP V, and after those MTP II, MCP III and MTP III [23]. This group also compared the proposed erosion score alone (Scoring by US Structural Erosion) to the Sharp score and found good correlation as well. In early RA, US was able to detect more erosions than radiography [24].

Taking the findings into account, a novel seven-joint US (US7) score for the use in daily rheumatologic practice was recently developed by Backhaus *et al.* The US7 score includes US examination of the following joints of the hand and forefoot: wrist, MCP II, III, PIP II, III, MTP II and V. These seven joints are assessed for synovitis, tenosynovitis/paratenonitis and erosions by grayscale and PD US of the side, which is clinically more affected by tenderness and/or swelling (clinically dominant). In this score,

synovitis and synovial/tenosynovial vascularity are scored semiquantitatively (grade 0–3). Synovitis in grayscale US is analyzed semiquantitatively as introduced by Scheel (see FIGURE 2 for the dorsal wrist examination by grayscale US) [19]. The PD US evaluation for synovitis and tenosynovitis/paratenonitis is scored after Szkudlarek (FIGURES 1 & 3) [18] and tenosynovitis/paratenonitis and erosions in grayscale US are registered as absent (0) or present (1) after OMERACT definition (FIGURES 3 & 4) [13]. The seven joints are assessed in a standardized manner according to German [14] and European League Against Rheumatism (EULAR) guidelines [15]. The novel US7 score has recently been evaluated in a German nationwide project in order to prove its value in the detection of disease activity and therapeutic response under daily rheumatologic condition. For that, 120 patients with RA (91%) and psoriatic arthritis (PsA; 9%) were examined at three visits (baseline and after 3 and 6 months) by using the US7 score. Seven joints of the clinically dominant hand and forefoot were assessed before (baseline) and after onset of therapy or change of actual therapy. In addition, the clinical DAS28 score and laboratory parameters (C-reactive protein [CRP] and erythrocyte sedimentation rate) were evaluated at each visit. US7 score, clinical and laboratory data significantly reduced after 3 (except PD US synovitis and erosion score) and 6 (except erosion score) months' onset or change of immunosuppressive therapy. Independently from different therapies (DMARDs and/or TNF-α inhibitors vs DMARDs alone) clinical, laboratory and US parameters improved. It was also demonstrated that the US7 synovitis score and DAS28 significantly correlated with each other through 3 and 6 months. The US inter- and intra-reader reliability of 30 readers taking part in this project was $\kappa = 0.55$ (synovitis in grayscale), $\kappa = 0.56$ (erosions), and $\kappa = 0.67$ (synovitis in PD). Consequently, this study presents that the novel US7 score is a feasible and suitable score for monitoring disease activity and response of therapy in daily rheumatologic practice [25]. Therefore, the US7 score should be implemented supplementary to DAS28, as only by US is differentiation between clinical and subclinical disease activity possible, so that future damage can be predicted [26,27].

Recently, Dougados *et al.* evaluated several ultrasonography synovitis scoring systems in comparison to clinical examination. In this study, 28 joints (DAS28), 20 joints (both MCP I–V and MTP I–V) and 38 joints (28 joints and MTP I–V) of RA patients were clinically and ultrasonographically (grayscale and PD US either binary or a 0–3 grade from dorsal) examined under 4-month anti-TNFα therapy. This multicenter study could not find US evaluation as an outcome measure more relevant than clinical examination [28].

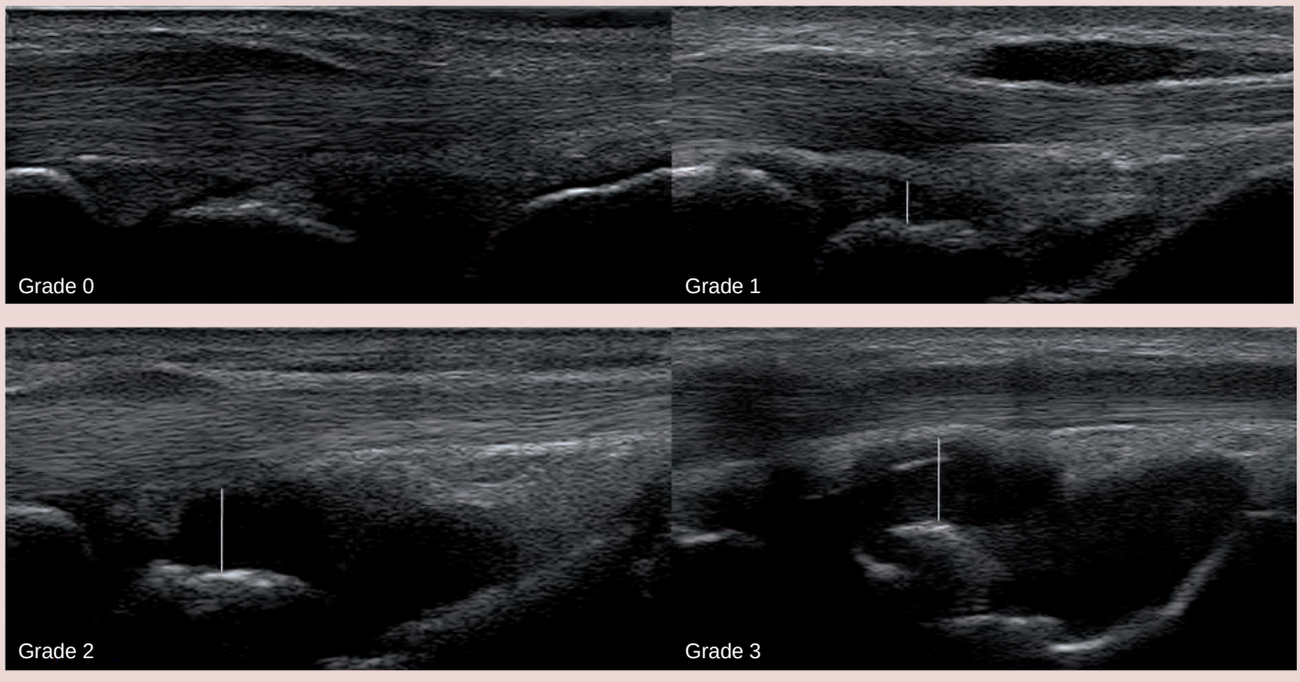

Figure 2. Synovitis in the dorsomedian wrist region by grayscale mode.

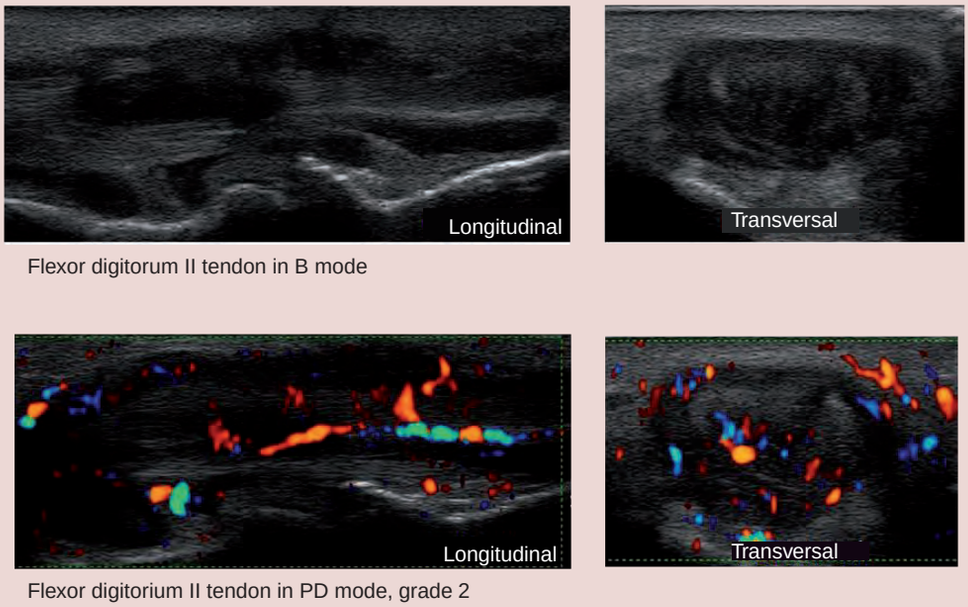

Figure 3. Tenosynovitis in grayscale and power Doppler mode.
PD: Power Doppler.

In the study by Ellegaard *et al.* the amount of color Doppler US in a single joint (in this case: wrist) was assessed in addition to clinical (DAS28, number of tender and swollen joints) and laboratory data (CRP, BSG) in 109 patients with RA. A significant correlation between color Doppler measurement and DAS28, swollen joint count, CRP, and erythrocyte sedimentation rate was found, concluding that one single affected joint can be used as a measure of disease activity [29].

Future perspective

In musculoskeletal US, scoring systems are used to monitor RA disease activity and the therapeutic response to disease-modifying antirheumatic drugs including conventional DMARDs and biologics. By utilizing semiquantitative systems the distension of the synovial/tenosynovial and erosive process can be estimated for each examined joint, whereas the use of US sum scores of a reduced joint count does have the advantage that overall disease activity is being reflected in a short examination time. In the development of US sum scores, Scheel *et al.* as well as Naredo *et al.* analyzed different numbers of joint scores, and both groups found that a reduced sum score is a useful tool in reflecting overall inflammatory activity in RA [19,20]. Both scores assess frequently involved joints in RA, but only including inflammatory signs such as synovitis (synovial hypertrophy and fluid) [19] and synovitis, effusion and PD activity, respectively [20]. The novel US7 score is the first to combine the examination of synovitis, tenosynovitis/paratenonitis and erosions in a composite sum scoring system detecting each feature separately. A high correlation of the US7 score to the clinical score DAS28 during treatment of DMARDs and/or TNF-α inhibitors over an examination time of 6 months was already presented. Furthermore, the US7 score allows, in contrast to the clinical score DAS28, the discrimination of different RA patient groups depending on disease activity and disease duration, respectively. A total of 201 patients with early (disease duration <2 years) and long-standing (disease duration ≥2 years) RA (95%) and PsA (5%) were examined by the DAS28 and the US7 score. Both patient groups had an initial moderate disease activity (4.8 and 4.9, respectively), but higher grayscale and PD synovitis scores were found in the patient group with long-standing disease duration of at least 2 years. Therefore, the US7 score is more sensitive for the examination of arthritic patients as it is able to identify disease activity by grayscale and PD US scores, although both patient groups were in similar clinical status [30]. A further analysis of the US7 score is necessary in order to optimize this sum scoring system. In the near future it has to be evaluated if there is a need to put in additional joint regions, that is, the dorsal part of the included finger joints MCP II, III and PIP II and III for the assessment of synovitis by

grayscale US examination, or even to exclude joint regions. So far, US examination for synovitis is mostly done only from the dorsal part of the finger joint although Scheel *et al.* discovered that synovitis was most frequently detected in the palmar proximal area (86%) of the affected finger joints [19]. This might be a reason for the study results presented by Dougados *et al.* in which US evaluation of synovitis (only assessed from dorsal) as an outcome measurement was not predominant to clinical examination [28]. A more detailed analysis regarding this point needs to be carried out. In a single joint analysis of the US7 score it was already demonstrated that paratenonitis of the finger joints is a rare finding in longstanding RA patients. In a group of longstanding arthritic patients (mean disease duration of 8.8 years) with RA (85.4%), PsA (12.2%) and spondyloarthritis (2.4%), paratenonitis was only found in one case. As a consequence, paratenonitis might not be a necessary component in the US7 score [31]. In the study by Ellegaard *et al.* assessment of one single affected wrist joint by color Doppler was only needed to measure disease activity [29]. For other joint regions and pathologies included in the US7 score a detailed analysis is being processed. The implementation of the US7 score in an early RA patient cohort needs to be evaluated in future studies, in order to prove its predictive value for therapeutic response to aggressive (biologic) or less aggressive (conventional DMARD) therapy and the outcome of the disease. Regarding this aspect, the US7 score might also play a role as a biomarker. For other sensitive imaging modalities this point is currently discussed [32]. Furthermore, the use of US sum score systems might predict re-therapies, especially in the therapeutic regime of anti-CD20 antibodies. The time point of re-therapy initiation in the treatment of RA by rituximab has not yet been objectified. In a group with RA patients receiving rituximab we could observe that grayscale and PD US scores already increased although clinical and laboratory data were still on a low level. Another important question is the implementation of an adequate US scoring system in Phase II and III studies that might objectively reflect treatment response of RA patients. Therefore, US would have a supplemental importance to the DAS28 or other clinical response criteria (i.e., ACR criteria) in clinical trials.

The current activities in the EULAR/OMERACT US group include the development of a Global OMERACT Sonography Scoring system in RA. The proof of its feasibility and value over standard clinical care is being processed. Global OMERACT Sonography Scoring system examines a number of small joints for synovitis, and the results evaluated by

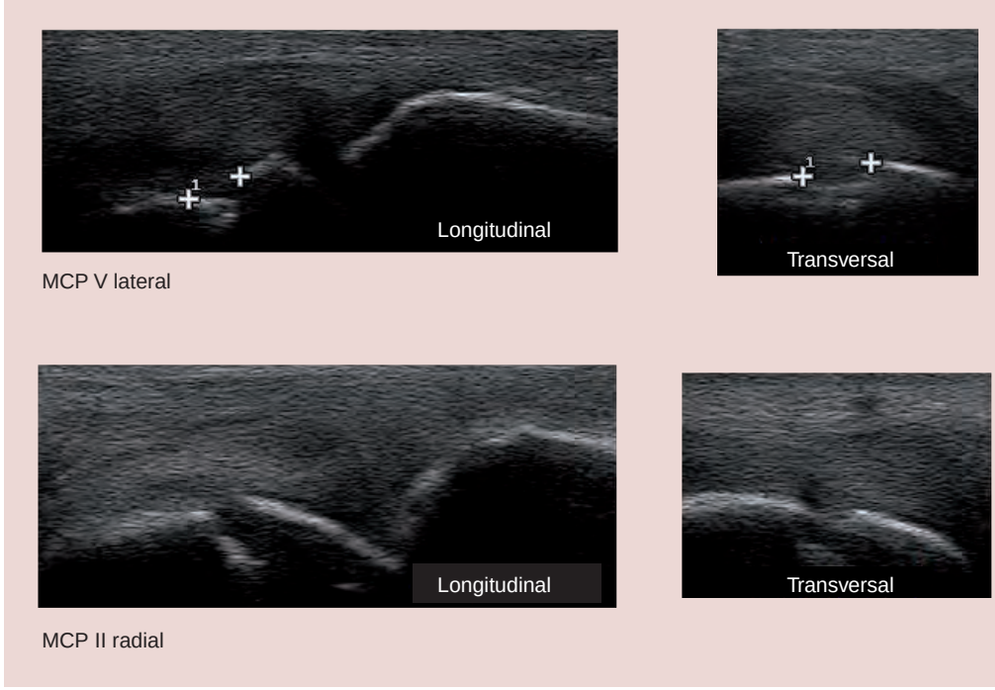

Figure 4. Erosions.
MCP: Metacarpophalangeal.

grayscale and PD US are combined as a sum in this scoring system [33]. Thus, differentiation between soft tissue alteration process ('soft tissue damage') by grayscale US and acute inflammatory soft tissue process ('soft tissue activity') by PD US, which is potentially reversible, is not possible. In our opinion, these two phenomena must be considered separately in one scoring system.

In summary, the implementation of musculoskeletal US as a patient-friendly, reliable bedside method in daily rheumatologic practice is very helpful and becomes more and more essential. The use of a representative US sum/composite scoring system containing active joint regions reduces examination time and, at the same time, reflects overall disease activity.

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Executive summary

Musculoskeletal ultrasonography: typical pathologies in rheumatoid arthritis

- Soft tissue lesions:
  - Synovitis (effusion and synovial hypetrophy/proliferation)
  - Tenosynovitis/paratenonitis
- Bone lesions:
  - Erosion

Sum/composite scoring systems in musculoskeletal ultrasonography

- Overall disease activity can be presented objectively in a short examination time.
- Implementation of ultrasound (US) in the daily rheumatologic practice is possible.
- US is used in monitoring new therapeutic regimes.

Conclusion

- US does have supplemental importance to clinical examinations/scores.
- US is objective and might have a predictive value (biomarker).
- Work in the future: development of an internationally accepted US sum scoring system.

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