OMERACT definitions for ultrasonographic pathology and elementary lesions of rheumatic disorders fifteen years on

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ABSTRACT

Objective. The Outcome Measures in Rheumatology (OMERACT) ultrasound (US) working group (WG) operates research activities for the validation of US as an outcome measurement instrument according to the Filter 2.0 framework

Methods. From the onset of the WG research in 2005 through now, original publications on definitions and scoring systems for pathophysiological manifestations and elementary lesions of various rheumatic disorders were reviewed

Results. Definitions and scoring systems according to new terminology are provided

Conclusions. We have redefined OMERACT definitions of US pathology and elementary lesions as well as scoring systems which are now proposed for OMERACT approval for application in clinical trials

INTRODUCTION

Since their introduction in 2005 [1], the use of the provisional ultrasound (US) definitions have become part of the fundamental Outcome Measures in Rheumatology (OMERACT) methodology for developing and validating US as a disease outcome measurement instrument (OMI) across various domains including inflammatory burden and structural damage [2,3].

In a seminal paper, the OMERACT ultrasound (US) working group (WG) described six provisional definitions of US lesions considered to represent a US core set of pathophysiological manifestations in rheumatic diseases [1]. The definitions were truly provisional, as at that time, a concurrent systematic literature review (SLR) highlighted the lack of consensus-based definitions in the existing literature [4].

Since then, iterative validation exercises have repeatedly shown US to be a reliable OMI for measuring (ir)reversible pathophysiological manifestations of RA, i.e., synovitis, tenosynovitis, or erosions [5,8]. Furthermore, the OMERACT US WG has engaged in the validation of US as an OMI by defining US manifestations of rheumatic disorders other than RA, including osteoarthritis, spondyloarthritis, psoriatic arthritis, crystal-related arthropathies, large vessel vasculitis, Sjogren's disease, systemic lupus erythematosus as well as in juvenile inflammatory arthritis. The validation process not only resulted in a

refinement of the original US definitions for RA pathologies but also in defining new disease-associated pathologies and corresponding elementary lesions.

This report provides an overview of the WG activities and presents the new US definitions and scoring systems for synovitis, enthesitis, tenosynovitis, and tendon damage.

UPDATED DEFINITIONS

a. Synovitis

Rather than defining a single entity, the initial definition included two elementary lesions, *synovial effusion* and *synovial hypertrophy*. Either one, separate or combined, could indicate synovitis [1].

Following a stepwise validation process that comprised a Delphi exercise for developing consensual definitions of pathology and elementary lesions, web-based and patient reliability exercises testing systematically the validity and the reliability of those lesions [5,6], a subtask force of the OMERACT US WG concluded that the old definition of synovitis was not sustainable. The "new" definition of an US-detected synovitis encompasses the whole concept of synovitis, thereby delineating synovial hypertrophy in a semi-quantitative graded B-mode feature and a graded Doppler mode feature. The presence of a hypoechoic SH is mandatory for defining the presence of an US-detected synovitis and for grading Doppler activity. Furthermore, the new definition lacks the elementary lesion ""synovial effusion",

since it did not prove reliable and also was frequently detected in healthy subjects [5-7]. In addition, the group developed a synovitis scoring system (5-7) combining B-mode and Doppler mode, which demonstrated sensitivity to change in small and large joints [8]. The new synovitis definition is presented in Table 1, and the new definition of the related elementary lesion is reported in table 2 . The combined EULAR-OMERACT scoring system is reported in the supplementary table 1.

b. Enthesitis

Whereas the provisional US definition spoke of enthesopathy [1], this term is now singled out exclusively for a mechanically-related tendinopathy or enthesopathy including sports-related activities [9,10].

Based on a SLR, a high variability was found in the definition of enthesitis and in particular, its constituent elementary components and no consensus-based scoring existed [9]. This inhomogeneity resulted in an appropriate task force to work on the development of a validated definition of enthesitis, using the same methodology described for developing synovitis [10,11]. The final definition of enthesitis is shown in table 1 and can be used in SpA and PsA, along with the elementary lesions that should be detected for defining such a pathological entity (table 2) and the scoring system to use for grading these elementary lesion [11]. The scoring of Doppler was further refined in a recent Delphi exercise (unpublished data) obtaining >75% consensus on a semi-quantitative scoring 0-3 (supplementary Table 2).

c. Tenosynovitis and tendon damage

Following the same systematic stepwise process, the OMERACT US WG conducted a series of formal Delphi studies and reliability exercises on elementary lesions of tenosynovitis and tendon damage, resulting in new definitions of tenosynovitis and related elementary lesions (table 1 and 2) as well as two scoring systems, one for tenosynovitis and one for tendon

damage (supplementary table 3) [12,13]. Tendon damage is a structural lesion and solely defined in B-mode, as this mode allows the evaluation of the morphology. Criterion validity of the tendon damage definition was demonstrated in cadavers [14]. The new definition of tenosynovitis includes changes in B-mode and Doppler mode and has shown sensitivity to change in patients with RA [15].

d. Bone erosion

The original OMERACT definition of bone erosion spoke of "an intraarticular discontinuity of the bone surface that is visible in two perpendicular planes" [1]. As no new definition has been developed, this definition is still valid (Table 1) [16]. Future research will focuss on distinguishing "true" RA- erosions from other cortical breaks, e.g. vessel channels.

e. Osteoarthritis (OA)

Initial activities on OA started as a joint venture between the OMERACT US WG and Osteoarthritis Research International and were mainly focused on structural abnormalities in hand OA. By testing the reliability of US in defining and grading cartilage lesions and osteophytes, the group produced a dichotomous and a four-grade semiquantitative score for cartilage damage and osteophytes, respectively (Table 2, supplementary table 3) [17,18]. Following the work on hand OA, the group targeted other joints [19].

f. Juvenile idiopathic arthritis (JIA)

Before defining synovitis in children, the JIA task force developed and validated definitions of normal joint components for different age groups through a Delphi consensus process and by testing them in a reliability exercise involving healthy children [20-23]. In contrast to the definition of synovitis in adults, the US definition in children also includes synovial

effusion [24]. The combined scoring system for synovitis using B-mode and PD mode is presented in Supplementary Table 4.

g. Gout

Following a SLR [25], the group conducted a Delphi exercise with the aim of obtaining and defining the elementary components of the gouty joint [26]. Four definitions of elementary lesions were highlighted, i.e., double contour, aggregates, tophus and erosions (Tables 1,2) and subsequently tested for reliability in a patient-based exercise [27]. Future work will determine if these elementary lesions are reliable in the development of a scoring system.

h. CPPD disease

Although no therapeutic drugs have been specifically developed for treating calcium pyrophosphate crystal deposit (CPPD) disease, the WG felt that CPPD related arthritis may be a confounding pathological manifestation. Following the OMERACT methodology, definitions of the US characteristics of CPPD at the level of fibrocartilage of the knee menisci and wrist, hyaline cartilage, tendons of the knee and synovial fluid of the knee were obtained (Table 2, supplentary table 5) [28]. Subsequently, a series of reliability exercises validated these elementary lesions [29].

i. Large vessel vasculitis (LVV)/giant cell arteritis (GCA)

The US appearance of normal temporal and extra-cranial large arteries (e.g., axillary arteries) and of respective lesions in vasculitis was defined [30](Table 2). As a result of the consensus exercises, the ‘halo sign’ and the ‘compression sign’ are regarded as the most important US abnormalities for GCA [31].

DISCUSSION

US is a unique OMI for rheumatic disease processes as it is capable to capture both the inflammatory state and the structural damage. Starting from the 2005 preliminary definitions, novel US definitions have been developed and validated by the US WG. In accordance with the Filter 2.0, the validation process of an US definition follows a stringent, step-by-step roadmap which comprises a SLR, a Delphi consensus process and patient reliability studies [2,3]. As the proof of the pudding is in the eating, responsiveness studies of US definition of synovitis and tenosynovitis have been carried out [8,15]. Along with progressive implementation of the OMI into clinical trials, patient feedback will enforce refinement of the application of US, which is in agreement with the current Filter 2.1.

The WG work is far from done. The bucket list now includes validating US as an OMI for monitoring disease activity in Sjogren's disease, musculoskeletal involvement of lupus, dactylitis in PsA (which remains one of the most challenging concepts to reliably capture by imaging), cartilage involvement in RA, and scleroderma. As to dactylitis, a definition of paratendinitis is currently an ongoing work.

In addition to the development and validation of new US definitions of different pathologies, further research needs to delineate the (minimal) discriminatory threshold of these US pathologies. The first attempt will be to define the threshold of an active synovitis in RA. Another important future activity will be the development of a reduced joint count based on the existing EULAR-OMERACT scoring system.

In conclusion, we have redefined OMERACT definitions of US pathology and elementary lesions These updated definitions will provide clarity as we complete the validation of these criteria and scoring systems which are now proposed for approval for application in clinical trials.

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Table 1. New OMERACT definitions of US-detected pathologies

Synovitis	Presence of a hypoechoic synovial hypertrophy regardless of the presence of effusion or any grade of Doppler signal
Enthesitis	Hypoechoic and/or thickened insertion of the tendon close to the bone (within 2 mm from the bony cortex) which exhibits Doppler signal if active and that may show erosions, enthesophytes/calcifications as sign of structural damage
Tenosynovitis	Abnormal anechoic and/or hypoechoic (relative to tendon fibers) tendon sheath widening which can be related both to the presence of tenosynovial abnormal fluid and/or hypertrophy. Doppler signal can be considered if seen in two perpendicular planes, within the peri-tendinous synovial sheath, excluding normal feeding vessels (i.e. vessels at the mesotenon or vinculae or vessels entering the synovial sheath from surrounding tissues). Doppler mode should be used only if the tendon shows peritendinous synovial sheath widening on B-mode
Tendon damage	Internal and/or peripheral focal tendon defect (i.e absence of fibers) in the region enclosed by tendon sheath, seen in two perpendicular planes; the grade of tendon damage should be assessed in both planes
Erosion	Intra- and/or extra-articular discontinuity of bone surface (visible in two perpendicular planes)
Pediatric synovitis	Presence of hypoechoic synovial hypertrophy or the presence of synovial effusion

Table 2. New definitions of the elementary lesions composing the US pathologies

Pathology	Inflammatory elementary lesion	Structural elementary lesion
Synovitis	Synovial hypertrophy is defined as presence of abnormal hypoechoic synovial tissue within the capsule that is not displaceable and poorly compressible and that may exhibit Doppler signals	
Enthesitis	Increased thickness of tendon at enthesis Hypoechoic tendon at enthesis Doppler signal<2 mm from bony surface	Calcifications/enthesophytes at enthesis Erosions at enthesis
Tenosynovitis	Tenosynovial hypertrophy is defined as presence of abnormal hypoechoic (relative to tendon fibers) tissue within the synovial sheath that is not displaceable and poorly compressible, and seen in two perpendicular planes; it may exhibit Doppler signals	
OA osteophytes		Step-up bony prominence at the bony margin that is visible in two perpendicular planes
OA hyaline cartilage damage		Loss of anechoic structure and/or thinning of cartilage layer, and irregularities and/or sharpness of at least one cartilage margin

Gout DC		Abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation which may be either irregular or regular, continuous or intermittent and can be distinguished from the cartilage interface sign
Gout Tophus		Circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (which may or may not generate posterior acoustic shadow), which may be surrounded by a small anechoic rim
Gout Aggregates		Heterogeneous hyperechoic foci that maintain their high degree of reflectivity, even when the gain setting is minimized or the insonation angle is changed and which occasionally may generate posterior acoustic shadow
CPPD fibrocartilage		Hyperechoic deposits of variable shape, localized within the fibrocartilage structure, that remain fixed or move along with the fibrocartilage during dynamic assessment

CPPD hyaline cartilage		Hyperechoic deposits of variable size and shape, without posterior shadowing, localized within the hyaline cartilage, that remain fixed and move along with the hyaline cartilage during dynamic assessment
CPPD tendon		Hyperechoic, linear structure(s) generally without posterior shadowing, localized within the tendon and remain fixed and move along with the tendon during dynamic assessment
CPPD synovial fluid		Hyperechoic deposits of variable size, localized within the synovial fluid, without posterior shadowing, and mobile along with joint movement and probe pressure
Halo Sign	Homogeneous, hypoechoic wall thickening, well delineated towards the luminal side, visible in two perpendicular planes, most commonly concentric in transverse scan	
Compression Sign	Thickened arterial wall remains visible under compression, i.e., the echogenicity contrasts hypoechogenic due to vasculitic vessel wall thickening in comparison to mid/hyperechoic surrounding tissue	

Abbrevations. CPPD, calcium pyrophosphate deposit; DC, double contour; OA, osteoarthritis; US, ultrasound.