The OMERACT Ultrasound Group: A Report from the OMERACT 2016 Meeting and Perspectives

Lene Terslev, Annamaria Iagnocco, George A.W. Bruyn, Esperanza Naredo, Jelena Vojinovic, Paz Collado, Nemanja Damjanov, Andrew Filer, Georgios Filippou, Stephanie Finzel, Frederique Gandjbakhch, Kei Ikeda, Helen I. Keen, Marion C. Kortekaas, Silvia Magni-Manzoni, Sarah Ohrndorf, Carlos Pineda, Viviana Ravagnani, Bethan Richards, Ilfita Sahbudin, Wolfgang A. Schmidt, Heidi J. Siddle, Maria S. Stoenoiu, Marcin Szkudlarek, Nikolay Tzaribachev, and Maria-Antonietta D'Agostino, on behalf of the OMERACT Ultrasound Group

ABSTRACT. Objective. To provide an update from the Outcome Measures in Rheumatology (OMERACT) Ultrasound Working Group on the progress for defining ultrasound (US) minimal disease activity threshold at joint level in rheumatoid arthritis (RA) and for standardization of US application in juvenile idiopathic arthritis (JIA).

Methods. For minimal disease activity, healthy controls (HC) and patients with early arthritis (EA) who were naive to disease-modifying antirheumatic drugs were recruited from 2 centers. US was performed of the hands and feet, and scored semiquantitatively (0–3) for synovial hypertrophy (SH) and power Doppler (PD). Synovial effusion (SE) was scored a binary variable. For JIA, a Delphi approach and subsequent validation in static images and patient-based exercises were used to developed preliminary definitions for synovitis and a scoring system.

Results. For minimal disease activity, 7% HC had at least 1 joint abnormality versus 30% in the EA group. In HC, the findings of SH and PD were predominantly grade 1 whereas all grades were seen in the EA cohort, but SE was rare. In JIA, synovitis can be diagnosed based on B-mode findings alone because of the presence of physiological vascularization. A semiquantitative scoring system (0–3) for synovitis for both B-mode and Doppler were developed in which the cutoff between Doppler grade 2 and grade 3 was 30%.

Conclusion. The first step has been taken to define the threshold for minimal disease activity in RA by US and to define and develop a scoring system for synovitis in JIA. Further steps are planned for the continuous validation of US in these areas. (J Rheumatol First Release February 1 2017; doi:10.3899/jrheum.161240)

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From the Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen; Department of Rheumatology, Zealand's University Hospital, Køge, Denmark; Dipartimento Scienze Cliniche e Biologiche — Reumatologia, Università degli Studi di Torino, Turin; Department of Medicine, Surgery and Neurosciences, Rheumatology Section, University of Siena, Siena; Pediatric Rheumatology Unit, IRCCS Ospedale Pediatrico Bambino Gesù, Rome; Internal Medicine Department, Azienda Socio Sanitaria Territoriale di Mantova, C. Poma Hospital, Mantua, Italy; Department of Rheumatology, MC Groep, Lelystad; Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands; Department of Rheumatology, Joint and Bone Research Unit, Hospital Universitario Fundación Jiménez Díaz; Autónoma University; Hospital Universitario Severo Ochoa, Madrid, Spain; Clinic Center, Faculty of Medicine, University of Niš, Niš; Institute of Rheumatology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; Rheumatology Research Group, The University of Birmingham, Birmingham; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds; UK National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK; Department of Rheumatology and Clinical Immunology, Faculty of Medicine, University of Freiburg, Freiburg; Charite University Hospital, Humboldt University; Immanuel Krankenhaus Berlin, Medical Center for Rheumatology Berlin-Buch; Pediatric Rheumatology Research Institute, Bad Bramstedt, Germany; APHP, Department of Rheumatology, CHU Pitie-Salpetriere, Paris 6 University, GRC-UPMC 08, Pierre Louis Institute of Epidemiology and Public Health; APHP, Hôpital Ambroise Paré, Rheumatology Department, 92100 Boulogne-Billancourt; INSERM U1173, Laboratoire d'Excellence INFLAMEX, UFR Simone Veil, Versailles-Saint-Quentin University, 78180 Saint-Quentin en Yvelines, Paris, France; Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan; Department of Rheumatology, Royal Perth Hospital, Perth, Australia; Instituto Nacional de Rehabilitacion, Mexico City, Mexico; Rheumatology Institute of Rheumatology and Orthopedics, Royal Prince Alfred Hospital, Camperdown, Australia; Department of Rheumatology, Université catholique de Louvain, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires Saint Luc, Brussels, Belgium.

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L. Terslev, MD, PhD, Center for Rheumatology and Spine Diseases, Rigshospitalet; A. Iagnocco, MD, Dipartimento Scienze Cliniche e

Biologiche — Reumatologia, Università degli Studi di Torino; G.A. Bruyn, MD, PhD, Department of Rheumatology, MC Groep; E. Naredo, MD, Department of Rheumatology, Joint and Bone Research Unit, Hospital Universitario Fundación Jiménez Díaz, and Autónoma University; J. Vojinovic, MD, PhD, Clinic Center, Faculty of Medicine, University of Niš; P. Collado, MD, Hospital Universitario Severo Ochoa; N. Damjanov, MD, PhD, Institute of Rheumatology, Faculty of Medicine, University of Belgrade; A. Filer, MD, PhD, Rheumatology Research Group, The University of Birmingham; G. Filippou, MD, Department of Medicine, Surgery and Neurosciences, Rheumatology Section, University of Siena; S. Finzel, MD, Department of Rheumatology and Clinical Immunology, Faculty of Medicine, University of Freiburg; F. Gandjbakhch, MD, APHP, Department of Rheumatology, CHU Pitie-Salpetriere, Paris 6 University, GRC-UPMC 08, Pierre Louis Institute of Epidemiology and Public Health; K. Ikeda, MD, PhD, Department of Allergy and Clinical Immunology, Chiba University Hospital; H.I. Keen, MD, PhD, Department of Rheumatology, Royal Perth Hospital; M.C. Kortekaas, MD, PhD, Department of Rheumatology, Leiden University Medical Center; S. Magni-Manzoni, MD, Pediatric Rheumatology Unit, IRCCS Ospedale Pediatrico Bambino Gesù; S. Ohrndorf, MD, Charite University Hospital, Humboldt University; C. Pineda, MD, Research Directorate, Instituto Nacional de Rehabilitacion; V. Ravagnani MD, PhD, Internal Medicine Department, Azienda Socio Sanitaria Territoriale di Mantova, C. Poma Hospital; B. Richards, MD, Rheumatology Institute of Rheumatology and Orthopedics, Royal Prince Alfred Hospital; I. Sahbudin, MD, Rheumatology Research Group, The University of Birmingham; W.A. Schmidt, MD, Immanuel Krankenhaus Berlin, Medical Center for Rheumatology Berlin-Buch; H.J. Siddle, MSc, PhD, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital; M.S. Stoenoiu, MD, PhD, Department of Rheumatology, Université catholique de Louvain, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires Saint Luc; M. Szkudlarek, MD, PhD, Department of Rheumatology, Zealand's University Hospital at Køge; N. Tzaribachev, MD, Pediatric Rheumatology Research Institute; M.A. D'Agostino, MD, PhD, APHP, Hôpital Ambroise Paré, Rheumatology Department, 92100 Boulogne-Billancourt, and INSERM U1173, Laboratoire d'Excellence INFLAMEX, UFR Simone Veil, Versailles-Saint-Quentin University.

Address correspondence to Dr. L. Terslev, Rigshospitalet Glostrup, Center for Rheumatology and Spine Disease, Ndr. Ringvej 57, Glostrup, 2600, Denmark. E-mail: terslev@dadlnet.dk

The recent Outcome Measures in Rheumatology (OMERACT) 2016 meeting held in Whistler, British Columbia, Canada, in May 2016 provided the opportunity for the OMERACT Ultrasound Working Group (WG) to present the new areas in which ultrasound (US) has progressed and the related validation process. Since the initiation of the group in 2004, the main focus over the past 12 years has been on validating US as an outcome measurement instrument, and an update of the group activities was recently published[1]. Initially, the US WG focused on rheumatoid arthritis (RA), but with the increasing use of US in other rheumatological conditions, the group expanded the validation work to new areas, which has led the US WG to form subgroups with individual focus areas. At the OMERACT meeting in Whistler, Canada, several subgroups presented their progress. The purpose of our report was to provide an update from 2 of the subgroups: the one working on the definition of US minimal disease activity in RA, and the pediatric subgroup, which is validating the use of US in juvenile idiopathic arthritis (JIA). Both subgroups have been working with pathophysiological manifestation (synovitis) in RA and JIA as the core domain according to the OMERACT filter 2.0[2].

Further development in RA

The US WG group has validated US in RA by defining elementary lesions such as tenosynovitis and synovitis, including its components[3,4], and developed and validated a consensus-based scoring system for synovitis and tenosynovitis for clinical trials[5,6,7,8,9,10] with a good sensitivity to change[11]. However, US elementary lesions such as synovial effusion (SE) and synovial hypertrophy (SH; with or without Doppler activity as a measurable sign of inflammatory activity) may be seen in healthy controls (HC)[12,13]. Therefore a threshold is needed for separating normal findings from pathology, thereby creating a definition for what may be perceived as minimal disease criteria. This will influence the definition of early disease onset, the optimal response to therapy, and the identification of US remission. The subgroup working on defining minimal disease criteria for RA presented data comparing US findings obtained in HC with US findings obtained from an early arthritis (EA) cohort with the aim of identifying which US elementary components are present in the joints of HC, their prevalence, and their preferred location, and how these differ from patients with EA. This comparison represents the first step in identifying the US findings clinically important in EA and to describe at joint level which US lesions should be considered pathological.

In the conducted study, US findings of SH, SE, and power Doppler (PD) in joints of HC and patients with EA were systematically documented, and the distribution and grading of the findings at joint level were compared to reassess the threshold of abnormality in regions of overlap.

The participants were recruited from 2 centers: the healthy subjects from Ambroise Pare Hospital, Boulogne-Billancourt, France, and the patients with EA from City Hospital and Queen Elizabeth Hospital, Birmingham, UK. The healthy subjects were excluded if they had previous or present signs of joint disease[13]. Patients with EA who were naive to disease-modifying antirheumatic drugs (DMARD) were included if they had ≥ 1 clinically swollen joint due to inflammatory arthritis as judged by a physician and symptom duration ≤ 3 months. DMARD-naive patients with EA were excluded if joint symptoms were solely attributed to osteoarthritis (OA). US was performed on the wrist and metacarpophalangeal 1–5 joints (MCP), proximal interphalangeal 1–5 joints (PIP), and metatarsophalangeal 2–5 joints (MTP), and SH and PD were scored semiquantitatively (0–3) using the consensus-based European League Against Rheumatism-OMERACT scoring system[9]; SE was scored as a binary variable.

The demographics results of the 2 cohorts are shown in Table 1.

In HC, 7% had at least 1 joint abnormality versus 30% in

Table 1. Demographics for the healthy subjects and patients with early arthritis.

Characteristics	Healthy Subjects	Patients with Early Arthritis
Patients, n	206	107
No. joints examined	6177	3210
Female, n (%)	146 (71)	60 (56)
Age, yrs, median (IQR)	32 (25–47)	51 (39–64)
Symptom duration, weeks (IQR)	NA	6 (4–8)

IQR: interquartile range; NA: not applicable.

the EA group. In HC, the abnormalities were seen in the wrist, MCP 1–4, and MTP 2–4, whereas SH and PD could be seen in all types of examined joints in the EA cohort, but SE was rare. In HC, the findings of SH were predominantly grade 1, although grade 2 and grade 3 could also rarely be found. In the EA cohort, all grades were seen, with grade 3 being most frequent in the MCP. For PD, only grade 1 was seen in HC, whereas grades 1–3 were seen in the EA cohort.

The next step is to determine a cutoff level and to study a group of healthy elderly participants, because the grade of synovial hypertrophy-like changes appears to be age-related[14].

Validating US in pediatrics

The increasing need for the use of US in pediatric rheumatology led to the formation of the pediatric subgroup. To test validity and to improve the applicability of US in JIA, in 2011–2012 the subgroup investigated the use of US among pediatric rheumatologists[15] and performed a systematic literature review[16], which highlighted face and content validity of US for detecting synovitis in JIA with higher sensitivity than clinical examination.

Then the subgroup defined and validated the components of healthy pediatric joints in a multistep consensus process involving a panel of international experts on musculoskeletal ultrasound (MSUS) in children.

In the first step, a group of experts joined a Web-based consensus process to develop definitions for the following components of the pediatric joint: hyaline cartilage, secondary ossification center, joint capsule, synovial membrane, and cortical ossified bone. A definition reaching ≥ 80% of agreement on a Likert scale from 1–5 was accepted[17].

In the second step, in a face-to-face meeting, a subgroup of these experts produced additional definitions for 2 joint components that were considered relevant in physiological vascularization of a pediatric joint, i.e., fat pad and physis, which were not described in detail in the previous definitions of pediatric joint components[18].

In the third step, the applicability of the previous and new definitions was tested in a live exercise involving healthy children. Following standardized image acquisition and machine-setting protocols, 4 joints (i.e., wrist, second MCP, knee, and ankle) were examined in 4 different age groups (toddler and preschool ages 2–4 yrs, young children ages 5–8 yrs, preadolescent ages 9–12 yrs, and teenager ages 13–16 yrs). Using $\varkappa$ statistics, the intraobserver agreement for the applicability of all definitions ranged from 0.44–1, and for the interobserver agreement ranged from 0.33–1, with highest agreement for the wrist and lowest for MCP 2. Thereafter, the 2 new definitions from the second step were agreed on through a Delphi process among a wider group of pediatric MSUS experts (manuscript in preparation).

Further, the group defined age-related findings, i.e., physiological vascularization and ossification grade in healthy children. In a live exercise with healthy children, it was shown that physiological vascularization can be detected with up to 3 solitary PD signals within the normal joint owing to physiological vascularization localized predominantly in the fat pad, the epiphysis, the physis, and the short bone cartilage. Additionally, the group developed an ossification grade definition in children[19].

Using the same methodology, the subgroup moved to define and validate the US elementary lesions in JIA and developed preliminary definitions for synovitis as presented in Table 2, in which synovitis can be based on B-mode findings alone, but not solely on the Doppler[20]. Taking this synovitis definition and the previously investigated physiological vascularization into account, the group developed a semiquantitative scoring system (0–3) for synovitis for both B-mode and Doppler mode through a Delphi process and a face-to-face meeting (manuscript in preparation). The scoring system was tested in a JIA patient-based exercise conducted in 2016. Scoring of synovitis is applicable only if synovial hypertrophy has been detected on B-mode. Doppler scoring differs from the Doppler scoring applied in adults[9], in which Doppler grade 2 and grade 3 are related to Doppler activity below or above 50% of the SH, respectively, whereas in children the cutoff between Doppler grade 2 and grade 3 is 30%.

The next step is to test the reliability of the scoring system and its sensitivity to change.

Table 2. Preliminary definitions for the sonographic features of synovitis in children.

Overarching principle: Synovitis detection by ultrasound in children includes the assessment of B-mode and Doppler mode (color or power Doppler) findings.

Synovitis can be detected on the basis of B-mode findings alone. Synovitis cannot be detected based on color/power Doppler findings alone.

- B-mode findings comprise synovial effusion and synovial hypertrophy.
- Synovial effusion is defined as an abnormal, intraarticular, anechoic, or hypoechoic material that is displaceable.
- Synovial hypertrophy is defined as an abnormal, intraarticular, hypoechoic material that is nondisplaceable.
- Color/power Doppler signals must be detected within synovial hypertrophy to be considered as a sign of synovitis.

Current perspectives

At the OMERACT 2016 meeting, new data were presented from the vasculitis subgroup, the RA in the foot and ankle subgroup, the gout subgroup, and the calcium pyrophosphate disease (CPPD) subgroup. The vasculitis and CPPD subgroups had performed systematic literature reviews and identified proposed definitions for elementary lesion in giant cell arteritis and in CPPD. After circulating these in Delphi exercises, agreements for the definitions of elementary lesions in vasculitis and CPPD were obtained.

Considerable progress has been made in the already existing subgroups for OA in the hand and foot, cartilage damage in RA, synovial biopsies, bone erosions and vessel channels, dactylitis, and psoriatic arthritis. The US group has also moved to new areas in rheumatology such as Sjögren syndrome and scleroderma, and initiated validation procedures.

APPENDIX 1. List of study collaborators. OMERACT Ultrasound Group: Philippe Aegerter, Sibel Aydin, Marina Backhaus, Arthur Bachta, Peter Balint, Hilde Berner Hammer, David Bong, Isabelle Chary-Valckenaere, Philip Conaghan, Eugenio De Miguel, Andrea Delle Sedie, Christian Dejaco, Emilio Filippucci, Jane E. Freeston, Walther Grassi, Marwin Gutierrez, Petra Hanova, Cristina Hernandez, Sandrine Jousse-Joulin, Fredrick Joshua, David Kane, Zunaid Karim, Gurjit Kealey, Juhani Koski, Damien Loeuille, Clara Malattia, Peter Mandl, Michaela Micu, Ingrid Möller, Johannes Roth, Nanno Swen, Ralf Thiele, Violeta Vlad, Richard J. Wakefield, and Daniel Windschall.

REFERENCES

1. Bruyn GA, Naredo E, Iagnocco A, Balint PV, Backhaus M, Gandjbakhch F, et al; OMERACT Ultrasound Task Force. The OMERACT Ultrasound Working Group 10 Years On: Update at OMERACT 12. J Rheumatol 2015;42:2172-6.
2. Boers M, Kirwan JR, Gossec L, Conaghan PG, D'Agostino MA, Bingham CO 3rd, et al. How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0. J Rheumatol 2014;41:1025-30.
3. Joshua F, Lassere M, Bruyn GA, Szkudlarek M, Naredo E, Schmidt WA, et al. Summary findings of a systematic review of the ultrasound assessment of synovitis. J Rheumatol 2007;34:839-47.
4. Wakefield R, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al; OMERACT 7 Special Interest Group. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005;32:2485-7.
5. Naredo E, D'Agostino MA, Wakefield RJ, Möller I, Balint PV, Filippucci E, et al; OMERACT Ultrasound Task Force. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis 2013;72:1328-34.
6. Bruyn GA, Hanova P, Iagnocco A, d'Agostino MA, Möller I, Terslev L, et al; OMERACT Ultrasound Task Force. Ultrasound definition of tendon damage in patients with rheumatoid arthritis. Results of a OMERACT consensus-based ultrasound score focussing on the diagnostic reliability. Ann Rheum Dis 2014;73:1929-34.
7. Gutierrez M, Schmidt WA, Thiele R, Keen H, Kaeley G, Naredo E, et al; OMERACT Ultrasound Gout Task Force group. International Consensus for ultrasound lesions in gout: results of Delphi process and web-reliability exercise. Rheumatology 2015;54:1797-805.
8. Terslev L, Gutierrez M, Christensen R, Balint PV, Bruyn GA, Delle Sedie A, et al; OMERACT US Gout Task Force. Assessing elementary lesions in gout by ultrasound: results of an OMERACT patient-based agreement and reliability exercise. J Rheumatol 2015;42:2149-54.
9. D'Agostino MA, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT Ultrasound Taskforce – Part 1: definition and development of a standardized scoring system. RMD Open (submitted).
10. Terslev L, Naredo E, Aegerter P, Wakefield RJ, Backhaus M, Balint P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT Ultrasound Taskforce – Part 2: reliability and application to multiple joints of a standardized consensus-based scoring system. RMD Open (submitted).
11. D'Agostino MA, Wakefield RJ, Berner-Hammer H, Vittecoq O, Filippou G, Balint P, et al; OMERACT-EULAR-Ultrasound Task Force. Value of ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results from the APPRAISE study. Ann Rheum Dis 2016;75:1763-9.
12. Terslev L, Torp-Pedersen S, Qvistgaard E, von der Recke P, Bliddal H. Doppler ultrasound findings in healthy wrists and finger joints. Ann Rheum Dis 2004;63:644-8.
13. Padovano I, Costantino F, Breban M, D'Agostino MA. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. Ann Rheum Dis 2016;75:1819-23.
14. Ellegaard K, Torp-Pedersen S, Holm CC, Danneskiold-Samsøe B, Bliddal H. Ultrasound in finger joints: findings in normal subjects and pitfalls in the diagnosis of synovial disease. Ultraschall Med 2007;28:401-8.
15. Magni-Manzoni S, Collado P, Jousse-Joulin S, Naredo E, D'Agostino MA, Muratore V, et al; Paediatric Ultrasound Group of the OMERACT Ultrasound Task Force. Current state of musculoskeletal ultrasound in paediatric rheumatology: results of an international survey. Rheumatology 2014;53:491–6.
16. Collado P, Jousse-Joulin S, Alcalde M, Naredo E, D'Agostino MA. Is ultrasound a validated imaging tool for the diagnosis and management of synovitis in juvenile idiopathic arthritis? A systematic literature review. Arthritis Care Res 2012;7:1011-9.
17. Roth J, Jousse-Joulin S, Magni-Manzoni S, Rodriguez A, Tzaribachev N, Iagnocco A, et al; Outcome Measures in Rheumatology Ultrasound Group. Definitions for the sonographic features of joints in healthy children. Arthritis Care Res 2015;67:136-42.
18. Collado P, Vojinovic J, Nieto JC, Windschall D, Magni-Manzoni S, Bruyn GA, et al. Toward standardized musculoskeletal ultrasound in pediatric rheumatology: normal age-related ultrasound findings. Arthritis Care Res 2016;68:348-56.
19. Windschall D, Collado P, Vojinovic J, Magni-Manzoni S, Balint P, Bruyn GA, et al. International multiobserver ultrasound reliability study of age-related vascularization and ossification in healthy children: the OMERACT Pediatric Ultrasound Task Force. Rheumatology (submitted).
20. Roth J, Ravagnani V, Backhaus M, Balint P, Bruns A, Bruyn GA; OMERACT Ultrasound Group. Preliminary definitions for the sonographic features of synovitis in children. Arthritis Care Res 2016 Oct 16 (E-pub ahead of print).