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Title: Stiffness: the cardinal symptom of inflammatory musculoskeletal diseases yet still variably measured: Report from the OMERACT 2016 Stiffness Special Interest Group

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Abstract

Objectives: The objectives of the OMERACT Stiffness special interest group are to characterize stiffness as an outcome in rheumatic disease and to identify and validate a stiffness patient-reported outcome (PRO) in rheumatology.

Methods: At OMERACT 2016, international groups presented and discussed results of several concurrent research projects on stiffness: a literature review of rheumatoid arthritis (RA) stiffness PRO measures; qualitative investigation into the RA and polymyalgia rheumatica patient perspective of stiffness; data-driven stiffness conceptual model development; development and testing of an RA stiffness PRO measure; and quantitative work testing stiffness items in RA and psoriatic arthritis patients.

Results: The literature review identified 52 individual stiffness PRO measures assessing morning or early morning stiffness severity/intensity or duration. Items were heterogeneous, had little or inconsistent psychometric property evidence and did not appear to have been developed according to PRO development guidelines. A poor match between current stiffness PROs and the conceptual model capturing the RA patient experience of stiffness was identified, highlighting a major flaw in PRO selection according to the OMERACT Filter 2.0.

Conclusion: Discussions within the Stiffness SIG highlighted the importance of further research on stiffness and defined a research agenda.

Key words: Stiffness, outcome measurement, OMERACT
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Running Title: Stiffness in rheumatic diseases
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**Statement of contribution to the literature:** We report an original literature review of stiffness patient-reported outcome measures in rheumatoid arthritis, and synthesis of international qualitative work investigating the patient experience of stiffness in rheumatic diseases presented at the OMERACT 2016 Stiffness special interest group session. This work advances current understanding regarding stiffness conceptualization and assessment across rheumatic conditions and represents original work.

**Original contributions of this article**

- An original literature review of stiffness patient-reported outcome measures in rheumatoid arthritis
- A synthesis of results from international qualitative work investigating the rheumatoid arthritis patient experience of stiffness in rheumatoid arthritis
- The first attempt to consolidate efforts regarding the understanding and assessment of stiffness in inflammatory rheumatic conditions

**Introduction**

Stiffness affects 70-75% of people with rheumatoid arthritis (RA) regardless of treatment status (1) and 44-80% of patients in low disease activity (2). Recent evidence shows that stiffness is important to patients with RA in flare (3) and remission (2) states, and it is an integral part of the RA experience (4, 5). Stiffness adversely affects health-related quality of life (6) and is associated with earlier initiation of disease-modifying therapy in RA (7). Furthermore, stiffness is a key symptom recognized by patients and clinicians in many other inflammatory rheumatic diseases including polymyalgia rheumatica (PMR) and psoriatic arthritis (PsA) among others (8-12). In RA, stiffness assessment is particularly relevant as it
likely influences patients’ ability to meet remission criteria (13). A recent systematic review (2) in RA low disease activity and remission identified and summarized the measurement properties of currently available stiffness patient-reported outcome (PRO) measures. The review identified only two articles, which made conflicting recommendations about the most appropriate concept for stiffness assessment (morning stiffness duration or severity), and concluded that there was insufficient scientific data supporting current stiffness measures (2).

The aim of the OMERACT 2016 stiffness special interest group (SIG) is to consolidate work on stiffness across inflammatory rheumatic conditions in order to systematize future research on the topic, and work towards identifying and validating an outcome measure for stiffness in rheumatic diseases that is consistent with methodology outlined by the OMERACT Filter 2.0 (14). In preparation for the Stiffness SIG at OMERACT 2016 the following research projects were conducted: 1) a literature review of stiffness PRO measure in RA; 2) a synthesis of qualitative research conducted in RA; 3) qualitative research with patients with PMR; 4) development, refinement and testing of candidate items for an RA stiffness questionnaire (15); and 5) examination of stiffness items in RA and PsA.

**Stiffness literature review**

A literature review was conducted to identify and assess measurement properties of stiffness PROs in RA. The search was conducted in PubMed using a validated search filter (16) and was consistent with a prior systematic literature review in RA remission (2), including articles identified there. Article screening determined 25 articles suitable for full text review (Figure 1). From these, 52 individual stiffness PRO measures were identified. All but one assessed morning stiffness or early morning stiffness. Most assessed the concepts of duration (n=30) or severity/intensity (n=18), while others assessed improvement (n=1), importance (n=1), and two were unclear. There was great variation in PRO wording, response options, format and timeframe. For example, PRO item formats included visual analogue scale (VAS) (n=14), numeric rating scale (NRS) (5), Likert scale (n=7), minutes in free text (n=23), and two items were unclear. Items were also poorly defined with 22 items unclear regarding some or all item
components. Reports of face, content, criterion and construct validity, reliability and responsiveness were limited and inconsistent. Overall, severity items appeared to perform better than duration items in relation to construct validity, discrimination between disease states, responsiveness, and sensitivity to change but evidence was limited. No articles reported the face or content validity of stiffness items and no patient involvement in item development was reported. A summary of the literature review findings is outlined in Table 1. In conclusion, current RA stiffness assessment is heterogeneous, incompletely reported and does not appear to have been developed according to PRO development guidelines recommending incorporating the patient perspective (42).

**Qualitative investigation of stiffness in RA**

A synthesis of qualitative work capturing the RA patient experience of stiffness was performed by an experienced qualitative researcher. The published papers reviewed (4) (5) reported two independent conceptual models based on inductive thematic analysis (43, 44) of international focus groups and semi-structured interviews. The synthesis identified six common domains (Figure 2). Patients considered stiffness a normal part of RA that was widely variable (in timing, duration and location) and did not occur exclusively in the mornings. Stiffness was related to other RA symptoms, impacted on daily life, and was influenced by external or personal factors (e.g. medication, self-management). The key, common concepts, that stiffness is not purely a morning symptom and is best evaluated by its impact (45), contrast with current stiffness assessments, which focus on morning stiffness severity or duration. This indicates a poor match between the conceptual model and currently used PROs, a major flaw according to OMERACT Filter 2.0 recommendations for selecting PROs (46).

**Qualitative investigation of stiffness in PMR**

Qualitative research was conducted in PMR to investigate the patient experience of stiffness and its assessment (47) through eight focus groups. The conceptual model of the PMR patient experience of stiffness had four major themes: ‘symptoms’, ‘functional impact’, ‘impact on daily
schedule’, and ‘approaches to measurement’. Stiffness was an important symptom for patients, distinct from pain, and for some it was ‘overwhelming’ and imposed restrictions on activities of daily life. For stiffness assessment, patients preferred an NRS or assessment of stiffness impact on daily life functioning rather than a VAS. Findings in PMR are consistent with qualitative work performed in RA. Assessing functional impact may be a pragmatic approach to difficulties with current stiffness assessments.

**Development of new RA stiffness questionnaire**

A new PRO for stiffness in RA has been developed based on qualitative research findings (4), qualitative investigation into the patient perspective of stiffness assessment, and an iterative process of item development involving clinicians, researchers and patients. Cognitive interviews with RA patients refined draft items into a set of 45 preliminary stiffness items. These were administered via a postal survey with additional PROs (patient global assessment VAS (48); pain NRS (49); Bristol Rheumatoid Arthritis Fatigue Severity NRS (50, 51); flare question from the Preliminary Flare Questionnaire (52); Modified Health Assessment Questionnaire (MHAQ) (53); Patient-based Disease Activity Score (54, 55)) and demographic questions to a new sample of patients with RA (n=277, 32.9% male, mean (SD) age 63.9 (12.4) years, range=23-97, median disease duration (IQR) 6 (3-15) years, range=1-45). Successive rounds of analytical refinement were performed using principal component analysis and Cronbach’s alpha for internal consistency to identify the smallest number of informative items. This resulted in the development of a new RA stiffness PRO measure (RAST) with 21 items and three components capturing stiffness ‘severity’, ‘physical impact’ and ‘psychosocial impact’ (15). The RAST PRO measure can now be tested in independent longitudinal studies to accumulate evidence on psychometric properties in RA and other rheumatic diseases.

**Quantitative testing of stiffness items in RA and PsA**
Stiffness items (severity, duration and impact) were assessed in a cross-sectional study of patients with PsA and age and sex-matched RA controls in the Australian Rheumatology Association Database (56), a voluntary national registry for patients with inflammatory arthritis. Stiffness items and additional PROs (MHAQ (53), pain, patient global assessment) were completed electronically by 103/158 patients with PsA and 111/158 with RA. Ratings of stiffness severity, duration and impact were comparable in RA and PsA. There was a high degree of correlation between different dimensions of stiffness (r=0.71-0.89) and stiffness item formats (r=0.58-0.90). Stiffness was independently associated with physical function in the multiple regression model. Stiffness severity and impact were most strongly associated with physical function (adjusted R²=0.60).

**Discussion**

Stiffness is an important symptom for patients across rheumatic conditions. It has been included in the RA Flare core domain set since 2014 and its inclusion in the PMR core domain set and the research agenda for PsA was endorsed at OMERACT 2016. Qualitative research and literature reviews demonstrate that current stiffness PROs may not adequately reflect stiffness dimensions that matter most to patients (2, 4, 5, 8). Hence, current stiffness items do not meet the OMERACT Filter 2.0 ‘eyeball test’ of being a good match with the domain of interest (46). Discussions within the SIG suggested that while stiffness is a generalizable domain across several rheumatic conditions, notable differences exist in the patient experience. For example, patients within the SIG highlighted that the location of stiffness would differ between PMR and RA and this should be reflected in the wording of items. This is also relevant in AS or PsA with axial spondyloarthritis. Possible solutions could include further qualitative investigation with different patient groups to tailor assessments to specific populations, or design of a comprehensive databank of stiffness items that can be administered using an interactive approach like computer adaptive testing. Meanwhile, research to develop and validate a comprehensive RA stiffness PRO measure is currently ongoing in the UK, US and Australia. This work has been grounded on qualitative research.
with patients and followed by item testing and refinement. Further testing and refinement in independent RA cohorts and additional rheumatic diseases is ongoing.

**Research agenda**

The OMERACT 2016 Stiffness SIG defined the following items on its research agenda: 1) investigation of contextual factors and adverse events which can be achieved through secondary data analysis of two qualitative datasets we collected in RA, PMR qualitative dataset as well as additional qualitative datasets (PsA); 2) qualitative investigation into the patient perspective of stiffness assessment in rheumatic diseases other than RA and PMR; 3) development and validation of stiffness assessment tools in RA. This may include further psychometric evaluations of the RAST and testing using item response theory; 4) investigation into stiffness pathophysiology across rheumatic conditions; and 5) review of stiffness assessment in osteoarthritis and non-rheumatic conditions to assess potential for integration with rheumatic disease stiffness.

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