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TITLE PAGE

Title:

Novel ultrasound joint selection methods using a reduced joint number demonstrate inflammatory improvement when compared to existing methods and Disease Activity Score (DAS28)

Authors:

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ABSTRACT

Objective

A pilot study testing novel ultrasound (US) joint selection methods in rheumatoid arthritis.

Methods

Responsiveness of novel (Individualized US (IUS) and Individualized-Composite-Ultrasound (ICUS)) methods were compared with existing ultrasound methods and DAS28 for 12 patients followed for 3 months. IUS selected up to 7 and 12 most ultrasonographically inflamed joints, while ICUS additionally incorporated clinically symptomatic joints.

Results

The existing, IUS, and ICUS methods' standardised response means were -0.39, -1.08, and -1.11, respectively for 7 joints; -0.49, -1.00, and -1.16, respectively for 12 joints; and -0.94 for DAS28.

Conclusion

Novel methods effectively demonstrate inflammatory improvement when compared with existing methods and DAS28.

Key Indexing Term: Rheumatoid Arthritis, Ultrasound, Synovitis

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Novel individualized ultrasound methods

INTRODUCTION

Ultrasonography is increasingly used to monitor joint inflammation in rheumatoid arthritis (RA) [1]. The optimal method selecting reduced joint counts for ultrasound monitoring is not established. Various criteria has been used for reduced joint selection (e.g. frequency of involvement/ feasibility/representativeness of joints/logistic regression models) [2]. Scanning fewer joints saves time [3] and yet can be representative of the inflammatory changes using extended scanning [4]. A systematic review studying ultrasound joint counts in RA [2] highlighted two existing methods [5,6] with good validity; one utilizing a pre-defined 7-joint count [5] and another utilizing a 12-joint count derived using ultrasound reduction from the frequency of inflammatory involvement from 44 joints [6]. As the extent and distribution of affected joints differs between individuals, such methods do not ensure selection of the most affected joints or the greatest number of affected joints per individual for ultrasound monitoring.

In our pilot study, novel individualized joint selection methods are designed to improve the number of affected joints per patient for ultrasound scanning (limited by a target joint number) The novel Individualized-Ultrasound (IUS) method selects up to 7 and 12 most inflamed joints detected on ultrasound, while the novel Individualized-Composite-Ultrasound (ICUS) method additionally incorporates clinically symptomatic joints. The key feature is joint selection dictated by severity, beginning with the most severely affected joint and continuing until the target count is reached. Target joint limits were set at 7 and 12 to maintain consistency with joint counts specified by existing methods [5,6]. We hypothesised that the novel methods would improve experimental efficacy resulting in greater sensitivity for detecting change when compared to existing methods and disease activity score 28 (DAS28).

METHODS

Patients

Seropositive RA patients (DAS28>3.2) with ≥ 5 tender and/or swollen joints starting or escalating DMARDs and corticosteroid therapy in the rheumatology unit at the Singapore General Hospital

were enrolled from March 2013 to May 2014 and followed up for 3 months. The local IRB approved this pilot study. Patients gave written informed consent. Patients with connective tissue diseases, other inflammatory arthritides, pregnancy, Hepatitis B/C, previous joint replacements or limb amputation were excluded.

At 0 and 3 months, a 44-joint clinical assessment (by a metrologist) and ultrasound were performed on the same day. A rheumatologist experienced in musculoskeletal ultrasound (blinded to the metrologist's findings) acquired and scored the ultrasound images.

Clinical assessment

Joints assessed for tenderness and pain included bilateral shoulders, elbows, wrists, metacarpophalangeal joint (MCPJ) 1-5, proximal interphalangeal joint (PIPJ) 2-5, thumb interphalangeal joint (IPJ), hips, knees, ankles, mid-tarsal, and metatarsophalangeal (MTPJ) 1-5. Of these 44 joints, 40 were assessed for swelling (hips and mid-tarsals excluded using the approach of DAS44 [7]). Joint tenderness and swelling were scored as 1=yes/0=no. Joint pain was scored as 0=none/1=mild/2=moderate/3=severe. These scores form the clinical sub-scores utilized in the ICUS method (further described under individualized methods).

Ultrasound evaluation

Ultrasonography was performed with General Electric Healthcare LOGIQe machine with a multi-frequency linear array transducer (5–13 MHz) or Philips Medical Systems EPIQ 5G machine with a multi-frequency linear array transducer (5–17 MHz). Ultrasound outpatient facility, machine, probe and settings were kept the same for each patient. Standardized scanning was based on the EULAR guidelines [8]. The joint/tendon sites scanned are listed in Table 1. Ultrasound pathology definitions from the EULAR OMERACT ultrasound workgroup were used [1]. Grey-scale synovial hypertrophy (SH) and power Doppler (PD) vascularity were scored semi-quantitatively (0=none/1=mild/2=moderate/3=severe) based on ultrasound scoring definitions

used by Backhaus et al [5]. This method was used at the hand and feet joints (as these joints were included in the study by Backhaus et al) and extrapolated for use in other joints (including the elbow, knee, ankle, mid-tarsal, shoulder and hip). However, at certain medium size joints (e.g. elbow, knee and ankle) whereby relevant images from a scoring atlas [9] are available, semi-quantitative scoring (0 to 3) was performed based on the relevant images from the scoring atlas. The shoulder and hip joints were not included in the original study by Backhaus et al nor the atlas, so where applicable, a score of 0 (normal) was taken to be grey-scale SH less than the mean plus 2 SD of normal range [10]. Tenosynovitis was scored as 1=yes/ 0=no for grey-scale and PD findings. These scores form the ultrasound sub-scores utilized in the existing and individualized methods (further described under the section existing methods and individualized methods).

Existing methods

The existing methods include the 7 and 12 joints used by Backhaus et al [5] and Naredo et al [6] respectively (see table 1). The individual joint score (IJS) per joint was calculated as the sum of the ultrasound sub-scores divided by the maximum possible score at that joint, so as to equalize score weights across the joints. The maximum number of affected joints selected by the existing 7 and 12 joints methods are therefore 7 and 12 respectively.

Individualized methods

In the 7-joint approach, the individualized methods select up to a maximum of 7 most affected joints for monitoring. In the 12-joint approach, the individualized methods select up to a maximum of 12 most affected joints for monitoring. For the IUS method, the IJS at each joint was calculated as the sum of the ultrasound sub-scores divided by the maximum possible score at that joint. For the ICUS method, the IJS at each joint was calculated as the sum of the clinical and ultrasound sub-scores divided by the maximum possible score at that joint. An affected joint for the existing and individualized methods was defined as $IJS > 0$.

The joint selection process (Figure 1) was as follows: the IJS from the 44 joints were ranked from

largest to smallest score. The target joint count was set at 7 and 12. Joints with the highest IJS were identified. Joint selection progressed from the small to medium and larger joints as described in Figure 1. This process was repeated utilizing joints with decreasing IJS until the target joint count was reached. The rationale for this joint selection process was: (1) RA frequently involves the small joints, (2) scanning small joints is often easier, and (3) the semi-quantitative scoring method was developed using smaller joints [11].

Statistical analysis:

For the above methods, the IJS from the selected joints were summed to obtain a total inflammatory score (TIS) per patient. Patients' mean TIS were calculated at 0 and 3 months and were used for deriving the standardized response mean (SRM), calculated as the mean change in the TIS score divided by the standard deviation (SD) of the change in the TIS score. The threshold values from Cohen for effect size (ES) are often used for interpretation, i.e. trivial ($ES < 0.20$)/small ($0.20 \leq ES < 0.50$)/moderate ($0.50 \leq ES < 0.80$)/large ($ES \geq 0.80$) [12-15]. The average number of affected joints at baseline by these methods was reported. The SRMs (at 3 months) were calculated for these methods and the DAS28.

RESULTS

Patient characteristics

12 RA patients [mean (SD) age 57.6 (6.5) years; 83.3% female; 83.3% Chinese, 8.3% Indian and 8.3% other ethnic groups] with mean (SD) disease duration at baseline of 55.8 (71.2) months completed the study. All patients were started or escalated on DMARDs and corticosteroid therapy prior to the baseline ultrasound scans. Within 3 months prior to recruitment, 8 (66.7%) patients were on oral DMARDs (which included methotrexate, sulfasalazine, hydroxychloroquine and azathioprine) while 11 (91.7%) patients were on prednisolone. The mean DAS28 at baseline and 3 months was 5.21 and 4.32, respectively. The SRM for DAS28 was -0.94.

7-joint and 12-joint approaches

Using 7 joints, the affected joints (average number) for the existing, IUS and ICUS methods were 3, 7 and 7, respectively, with corresponding SRMs of -0.39, -1.08 and -1.11.

Using 12 joints, the affected joints (average number) for the existing, IUS, and ICUS methods were 7, 11 and 12, respectively. The SRMs were -0.49, -1.00 and -1.16 respectively (Table 2).

DISCUSSION

Our novel methods using a reduced joint number effectively demonstrate inflammatory improvement when compared to existing methods and DAS28. This is unsurprising, given our emphasis on selecting affected joints (i.e. selecting as many affected joints, beginning with the most severely affected ones, until the target joint limit is reached) for follow-up scanning.

The SRM of the existing methods was consistent with the SRMs reported in two RA studies [15, 16] using ultrasound monitoring. The SRM was -0.2595 at 5 months in one study [15] utilizing ultrasound of bilateral MCPJs 1-5 and -0.46 at 3 months in another study [16] utilizing ultrasound at the dominant wrist.

Our individualized methods required a 44-joint ultrasound assessment at baseline to select the target joints. While this means additional time at the baseline scan, follow up scans require less time when compared to the baseline scan as only the selected joints need rescanning.

Our pilot results will need to be confirmed in larger cohorts. Future studies incorporating control group(s) for comparison, as well as correlation with other patient outcomes (e.g. disease remission/structural alteration/ functional prognosis) would be necessary. The number of reduced joints to assess during follow-up could also be explored in larger studies.

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