The relation between composite ultrasound measures and the DAS28 score, its components and acute phase markers in adult RA

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Objectives. Ultrasound (US) provides measurements of synovial morphology and vascularity. However, on an individual joint basis in RA, US measures do not relate well to clinical signs. This study investigates the relationship between composite US measures and the 28-joint disease activity score (DAS28), its components and acute phase markers in adult RA.

Methods. RA synovial disease activity was recorded in 50 patients by: (i) the DAS28 score; (ii) ESR and CRP; and (iii) US using Grey scale (GS) and power Doppler (PD) measures of PIP and MCP joints to derive composite US scores based on abnormal counts and severity. A total of 25 control subjects were studied to define normal US appearances. The relation between each measure of synovial disease was determined by Spearman correlation analysis.

Results. There was a significant relation between the DAS28 and the GS joint count (GSJC, Spearman’s r = 0.4; P = 0.004) and severity score (GSJS, r = 0.34; P = 0.016) and the PD joint count (PDJC, r = 0.32; P = 0.028). There was a significant relation between the ESR and PDJC (r = 0.37; P = 0.007) and PD joint severity score (PDJS, r = 0.38; P = 0.006) and between the CRP and PDJS (r = 0.29; P = 0.04). The remaining components of the DAS28 related poorly to all US measures, except the tender joint count, which related significantly to the GS but not the PD measures.

Conclusions. Composite US markers of synovial disease relate significantly to the DAS28 score and ESR/CRP in adult RA, but not as well with individual clinical joint counts and the patient’s global assessment.

Key words: Rheumatoid arthritis, DAS28 score, Ultrasound, Power Doppler, Disease activity assessment.

Introduction

In RA, sustained high disease activity results in a poor outcome, from the perspective of musculoskeletal health [1], and life expectancy [2]. Successful management aims to suppress inflammation, with regular assessments of disease activity determining appropriate treatment. There is no gold standard for this purpose, but rheumatologists in the EU have widely adopted the composite 28-joint disease activity score (DAS28) to assess RA disease activity in daily practice [3]. The DAS28 score provides a numeric index, in which a score >5.1 implies high disease activity (and is one of the prerequisites in the UK for commencing biologic therapies), a score <3.2 indicates low disease activity and a score <2.6 indicates remission, comparable with the ARA remission criteria [4]. A low DAS28 score over time reduces the probability of progression of radiological joint damage [5, 6]. Thus, the DAS28 appears to be a valid aid in determining and evaluating disease status in RA. Nevertheless, the DAS28 needs to be interpreted with some caution, given the subjectivity of clinical assessments and the potential for a very high tender joint count [7], or small changes in ESR at the low end of the reference range [8] to disproportionately affect the score.

High-resolution ultrasound (US) is being increasingly applied to the analysis of RA [9, 10]. Grey scale (GS) US is used for visualization of joint structures, enabling a distinction between synovial hypertrophy and other causes of apparent joint swelling such as subcutaneous oedema or tenosynovitis [11–13]. Power Doppler (PD) allows an assessment of synovial vascularity and hence a distinction between inflamed and non-vascular synovial swelling. In RA, PD imaging of knee synovial vascularity correlates well with histological factor VIII expression [14], and with gadolinium (static and dynamic)-enhanced MRI images of knee and MCP synovitis [15, 16].

It has become clear that there is a poor relation, on an individual joint basis, between clinical signs of synovitis (joint swelling and tenderness) and both GS and PD measures of synovial disease [17]. US detects far more synovial hypertrophy than is palpable [17, 18], and PD demonstrates that not all swollen and/or tender joints are necessarily hypervascular, yet a clinically normal joint may contain abnormally vascular synovial tissue [17]. Discrepancies between clinical and US measures in individual joints may be overcome by composite counts or scores from several joints, which taken together may be more representative of total disease activity in the patient. Therefore, we have explored this relation by comparing the DAS28 and its components, including the ESR and CRP, with composite GS and PD US counts and scores from the MCP and PIP joints in RA.

Patients and methods

Patients

Fifty patients fulfilling the 1987 ARA criteria for RA [19] were recruited from the Rheumatology Department of St George’s Hospital, London, UK. The patients’ mean age was 60 yrs (range 26–85), 39 were females, mean RA duration was 11 yrs (range 9 months–36 yrs), 40 patients were positive for RF and 38 had erosive disease.

The Wandsworth Research Ethics Committee approved the study and all patients and control subjects gave written informed consent.

Clinical assessment

The DAS28 score [3] was determined for each patient. The swollen and tender 28-joint count (SJC28 and TJC28, respectively) was performed by two clinicians, and the final score agreed by consensus, according to standard criteria [20].

Blood was taken for ESR and CRP analysis by standard laboratory techniques. The possibility of co-existent infection driving the inflammatory response was excluded by asking structured screening questions, performing physical examination and urine analysis. Patients were excluded from the study if...
symptoms or signs suggested infection or their urine dipstick was positive for nitrites.

**US protocol**

Immediately after clinical examination, the MCP and PIP joints were scanned using a Philips HDI 5000 (Philips Medical Systems, Andover, MA, USA) with a C7-15 MHz ‘hockey-stick’ transducer. For the PD studies, the Doppler settings were optimized to ‘Low flow’, with a medium wall filter (to minimize flash artefact) and a pulse repetition frequency of 700 Hz. The colour gain was adjusted to just below the noise floor and remained at this level throughout the scanning protocol. Each joint was held at 20° of palmar flexion and scanned from the dorsal surface, in both longitudinal section (LS) and transverse section (TS).

In each patient, 20 joints (10 PIP and 10 MCP joints) were scanned and scored by one of the two experienced musculoskeletal ultrasonographers. For each joint a separate GS and PD subjective score was recorded (Table 1) in a standard manner ranging from 0 to 3 (21–24). Scores of 0 were considered normal, and 1, 2 or 3 abnormal. From this the following composite US measures of synovial disease were made:

(i) GS joint count (GSJC): the number of joints scoring either 1, 2 or 3, out of a total of 20.
(ii) GS joint score (GSJS): the sum of the GS scores in all 20 joints, out of a total of 60.
(iii) PD joint count (PDJC): the number of joints scoring either 1, 2 or 3, out of a total of 20.
(iv) PD joint score (PDJS): the sum of the PD scores in all 20 joints, out of a total of 60.

Thus, the GSJC and PDJC simply reflected a normal or abnormal appearance, akin to the SJC and TJC system used in the DAS28, whereas the GSJS and PDJS incorporated a measure of severity.

Blinding was maintained throughout the data collection such that the clinicians and radiologists were unaware of each other’s findings.

The relationship between US measures and clinical or serological measures of synovial disease was determined between: the US measures and the DAS28 score, the DAS28 components, the ESR and the CRP. An analysis was also made between the US measures and the SJC and TJC from the 20 MCP and PIP joints (SJC20 and TJC20, respectively), as opposed to the full 28 joints that make up the DAS28.

**Statistical analysis**

Spearman correlation was used to compare continuous variables using GraphPad Prism software version 4.03 (GraphPad Software, San Diego, CA, USA).

**Control subjects**

To determine the range of appearances in normal MCP joints on PD, 25 control subjects with no history or clinical signs of joint disease were recruited. The mean age was 45 yrs (range 24–62) and 17 were females. Each MCP joint was immediately scanned according to the same protocol and any synovial thickening or PD signal scored. The GS appearances were grade 0 in 247/250 joints, with grade 1 appearances in three joints, from two male subjects aged 26 and 34 yrs. There was a history of manual occupation in both subjects. The PD appearances were grade 0 in 237/250 joints, with grade 1 appearances in the remaining 13 joints in 8 subjects (mean age 48 yrs). In four of these subjects, there was a history of manual work or GS findings of early OA. In the remaining subjects, there was no clinical or US explanation for this PD score, but in all 13 joints the score was only just grade 1, with a single (rather than several) vessel colour dot seen.

**Results**

**RA patients**

Range of clinical, serological and US measures of synovial disease. All screened patients consented to take part in the study and on the day of data collection none were found to have features of intercurrent infection. Within the cohort of 50 patients there was a wide range of scores in each of the individual measures of synovial disease (Table 2), demonstrating a broad spectrum of disease activity in recruited patients.

In the 50 patients, 1000 PIP and MCP joints were examined and scanned in total. Of these, there were 269 clinically swollen joints and 351 clinically tender joints. The distribution of US scores was GS score 0: 94; 1: 319; 2: 426; 3: 161; PD score 0: 565; 1: 205; 2: 184; 3: 46. Thus, abnormal synovial thickness was seen in 906/1000 joints with GS score 1 or 2, and increased PD signal was seen in 435/1000 joints (score 1, 2 or 3). Therefore, US detected more synovial hypertrophy than did clinical examination, and more joints had an abnormal PD signal than were clinically tender or swollen.

**Relation between US and serological measures of synovial disease.** A significant correlation was found between the ESR and PDJS (r = 0.38; CI 0.11, 0.6; P = 0.006, Fig. 1) and PDJC (r = 0.37; CI 0.1, 0.6; P = 0.007), and between the CRP and PDJS (r = 0.30; CI 0.05, 0.53; P = 0.04, Fig. 2) but not PDJC (r = 0.23; P = 0.06). This relation was weaker between the ESR and GSJC [r = 0.25, not significant (NS)] and GSJC (r = 0.11, NS) and between the CRP and GSJS (r = 0.26, NS) and GSJC [r = 0.05, NS].

**Relation between US and clinical measures of synovial disease.** A significant correlation was found between the DAS28 score and the US measures of synovial disease. The relation was strongest with the GSJC (r = 0.4; CI 0.12, 0.61; P = 0.004) and the GSJS (r = 0.34; CI 0.05, 0.57; P = 0.01, Fig. 3), and also significant with the PDJC (r = 0.32; CI 0.04, 0.55; P = 0.03) but not the PDJS (r = 0.26, NS).

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**Table 1. Subjective GS and PD scoring system for US images of MCP and PIP joints, derived from an assessment of images in both longitudinal and transverse planes**

<table>
<thead>
<tr>
<th>GS synovial score</th>
<th>PD score</th>
</tr>
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<tbody>
<tr>
<td>0 Absence of synovial hypertrophy</td>
<td>Absence of PD signal</td>
</tr>
<tr>
<td>1 Small degree of synovial hypertrophy</td>
<td>Single vessel dots</td>
</tr>
<tr>
<td>2 Moderate synovial hypertrophy</td>
<td>Confluent vessel dots over less than half the area of synovium</td>
</tr>
<tr>
<td>3 Marked synovial hypertrophy</td>
<td>Confluent vessel dots over greater than half the area of synovium</td>
</tr>
</tbody>
</table>

**Table 2. The range, mean and s.d. of clinical, serological and US measures of synovial disease in 50 patients with adult RA**

<table>
<thead>
<tr>
<th>Disease activity score</th>
<th>Range</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>2.87–7.33</td>
<td>5.2</td>
<td>1.1</td>
</tr>
<tr>
<td>SJC28</td>
<td>0–17</td>
<td>7.3</td>
<td>4.1</td>
</tr>
<tr>
<td>TJC28</td>
<td>0–26</td>
<td>10.6</td>
<td>6.7</td>
</tr>
<tr>
<td>SJC20</td>
<td>0–14</td>
<td>5.4</td>
<td>3.6</td>
</tr>
<tr>
<td>TJC20</td>
<td>0–20</td>
<td>7.5</td>
<td>5.9</td>
</tr>
<tr>
<td>VAS</td>
<td>5–90</td>
<td>49.2</td>
<td>17.9</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>2–81</td>
<td>31.4</td>
<td>21.5</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1–90.7</td>
<td>14.6</td>
<td>17.8</td>
</tr>
<tr>
<td>GSJC</td>
<td>0–20</td>
<td>12.6</td>
<td>5.9</td>
</tr>
<tr>
<td>GSJS</td>
<td>7–55</td>
<td>34.6</td>
<td>10.7</td>
</tr>
<tr>
<td>PDJC</td>
<td>0–19</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>PDJS</td>
<td>2–51</td>
<td>13.2</td>
<td>10.2</td>
</tr>
</tbody>
</table>

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Amongst the individual clinical components of the DAS28 score [TJC28, SJC28, visual analogue scale (VAS)] there was a significant relation between the TJC28 and the GSJC \((r=0.38; \text{CI 0.1, 0.6; } P=0.006)\) and a weaker relation with the GSJS \((r=0.25, \text{NS})\). There was no significant relation between the SJC28 or VAS and any of the GS or PD measures. The TJC20 (i.e. limited to the 20 scanned MCP and PIP joints) also related significantly to the GSJC \((r=0.5; \text{CI 0.24, 0.68; } P=0.0003)\) and the GSJS \((r=0.31; \text{CI 0.03, 0.55; } P=0.03)\), but only weakly to the PDJC \((r=0.26, \text{NS})\) and the PDJS \((r=0.17, \text{NS})\). There was no significant relation between the SJC20 and any of the GS or PD measures.

Discussion

In this explorative study, we aimed to compare the information derived from composite clinical and serological measures of RA disease activity with composite information from US, in 20 MCP and PIP joints per patient. There was a consistently significant relation between the DAS28 score and three of the four US measures, in 20 MCP and PIP joints. There was a significantly stronger relation with the GS than the PD measures, and the association was stronger with the count than the severity score, for both GS and PD. Amongst the clinical components (SJC, TJC, VAS) only the TJC related significantly to any of the US measures, and as with the DAS28 the association was stronger with the GS than the PD measures and stronger with the count than the score. In contrast, the ESR and CRP were more closely related to the PD measures than the GS measures, and here the PDJS showed a slightly stronger relation to both the ESR and CRP than the PDJC.

The closer relation between the ESR or CRP and the PD measures as opposed to the GS measures might be predicted as PD provides a measure of vascularity and hence inflammation, whereas GS demonstrates abnormal synovial morphology. In contrast, it is interesting that the GS measures (both count and score) should relate more closely to the DAS28 and the TJC than the PD measures. This raises questions as to the significance of PD signal within the RA joint. Whilst vascularity is an early and persistent feature of the inflamed RA synovium, and is associated with bone damage [25], its distribution and intensity seemingly does not directly relate to traditional clinical scores of RA disease activity (i.e. the DAS28 and its components). Long-term prognostic studies will be required to determine which best predicts the radiological and functional outcome, and recent data suggest that time-integrated PD measures may be better than clinical and laboratory parameters in early disease [26].

We restricted the US examination to 20 joints, rather than all 28 joints that make up the DAS28 score, because the bulk of the disease is often found in MCP/PIPs and time constraints would have made a 28 joint assessment by US impractical, particularly if this were to be translated to a routine clinical setting. This decision may limit interpretation of the associations between clinical/serological and US data in those patients with marked synovial disease in the omitted relatively larger eight joints (wrists, elbows, shoulders, knees) which in turn could disproportionately contribute to the systemic acute phase response. However, in the cohort studied, there was a wide range of disease activity and ESR/CRP scores and the mean SJC28 and TJC28 was only 1.6 and 3.1 joints more than the SJC20 and TJC20, respectively (Table 2). Furthermore the most consistent significant associations were found between the DAS28 and the US measures, in contrast to the DAS28 components where the SJC20 and SJC28 showed no significant associations with any of the US measures, and the TJC20 and TJC28 were associated with the GS but not the PD measures. Therefore, the restriction of the US measures to 20 MCP and PIP joints does not appear to have masked a relation with the composite DAS28 score.

As a technique, the use of US to image the synovium and assess its vascularity in an individual joint is fairly straightforward; however, the translation of this information into a meaningful assessment of global RA disease activity is complex. If US is to be used in routine clinical practice, time and technology constraints mean that a simply derived score such as the subjective 0–3 scale used in this study is attractive. Although this has been widely adopted [21–23, 27, 28], the boundary of normal vs. abnormal for
the purpose of a joint counting exercise (GSJC, PDJC), akin to clinical counts, has not been agreed. It is not clear in the literature where the cut-off between normal and abnormal lies on this 0–3 scale for GS or PD images, either from a histological perspective or in relation to future disease progression. In one study of healthy finger joints, a score of 0 or 1 was deemed normal whereas 2 or 3 was abnormal, using an Acuson Sequoia US machine [28]. This interpretation has been adopted by some [23, 24, 29] but not all other centres, where the definition of abnormal has been placed as ≥1 [30]. Each centre has used US equipment of differing sensitivity. In this study, we have used a control cohort to determine normal GS and PD appearances on our Philips HDI 5000 US machine. Our findings with this equipment in 250 clinically normal MCP joints lead us to conclude that a GS and PD score of 1, 2 or 3 is abnormal. Therefore, differing US definitions of normal are likely to reflect the sensitivity of the US equipment used, and as such the use of composite US joint counts needs to be standardized to the equipment used.

To overcome the problem of defining ‘normal’ the sum of the US scores per joint was used to derive a composite severity score. This has the potential advantage over a simple normal/abnormal count of both incorporating a measure of severity in the total score, and avoiding the need to categorize a joint as normal or not. Our results show that this was reflected in the associations between the ESR/CRP and US measures, as these were stronger for the joint scores than the counts (except the ESP and PDJS/ PDJC where the relation was virtually identical). In contrast, when related to the DAS28 and the TJC (where both assessments are based on clinical counts) both GS and PD joint counts showed stronger associations than the GS and PD scores. If the data are re-analysed using a threshold where 0 and 1 are normal, the association between the DAS28 and PDJC or GSJC becomes weaker than the PDJS and GSJS. This demonstrates the critical importance of determining the threshold between normal and abnormal when calculating the US joint count, and underscores the need to standardize data with controls using the same sonographers and equipment.

In a similar study to ours, Naredo et al. [22] compared ESR, CRP, VAS and clinical features of disease activity with US findings in 60 joints of 94 patients with RA. In keeping with our findings, there was a closer relation between US measures (GS and PD) and CRP/ESR than VAS. Amongst the clinical measures, the tender joint count did not relate to US measures whereas joint swelling did, and here a clinical swollen joint index (taking into account severity) related more closely to the US measures than did the simple SJC. No comparison with the DAS28 was made. In contrast, using a similar technique and scoring system for wrist, MCP and PIP joints in 47 RA patients, Weidekamm et al. [23] reported a significant correlation between PD scores and clinical findings but not ESR or CRP. Both studies employed different US equipment to ours.

Correlations observed in our study between the US scores and the DAS28 score, ESR and CRP were generally weak. This may reflect the inclusion of patients with long-standing disease (where joint swelling is not always a reliable finding) and the relatively small sample size. In Naredo’s cohorts, stronger correlations were found with a sample size twice as large [22] and in early disease [26]. Similarly, others with smaller samples have found weak correlations [23, 27, 31]. However, Szkuudlarek et al. [16] describe much tighter correlations between US and MRI measures of synovial disease, than US and clinical measures, and it is interesting that a weak association also holds for MRI and clinical measures [32].

A further possible explanation for the relatively weak relation between imaging modalities and clinical signs (either on an individual joint basis or composite scores) is the striking heterogeneity in clinical patterns of RA disease, whereby joint counts, VAS scores and acute phase markers are not necessarily proportionately matched in all patients. Thus, some patients with erosive disease may never have a high acute phase response, whereas others remain non-erosive despite persistently high joint counts. Such ‘outliers’ were clearly demonstrated in this study, with some patients demonstrating high US scores but low clinical indices and vice versa. Composite scores of disease activity aim to compensate for such heterogeneity, and indeed in this study and others [31], a hierarchy of relation to US measures has been found, in which ESR, CRP and DAS28 generally correlate better than the individual clinical signs or VAS.

It remains to be determined whether US can predict long-term disease progression, joint erosions and preservation of function better than traditional clinical or serological scores. Until then the DAS28 score is likely to remain a useful tool in clinical practice, but in situations where the DAS28 score, acute phase markers or the global assessment of disease activity are discordant, US may provide useful information regarding synovial disease and vascularity.

References


