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CONCISE REPORT

Persistence of subclinical sonographic joint activity in rheumatoid arthritis in sustained clinical remission

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ABSTRACT

Background Sonographic assessment, measuring grey scale (GS) and power Doppler (PD) signals, is a sensitive tool for the evaluation of inflammatory joint activity in patients with rheumatoid arthritis (RA). We evaluated the persistence of PD and GS signals in previously clinically active RA joints that have reached a state of continuous clinical inactivity.

Methods We performed sonographic imaging of 22 joints of the hands of patients with RA, selected all joints without clinical activity but showing ongoing sonographic signs of inflammation, and evaluated the time from last clinical joint activity.

Results A total of 90 patients with RA with 1980 assessed joints were included in this study. When comparing the mean time from clinical swelling, we found a significantly longer period of clinical inactivity in joints showing low sonographic activity (mean±SD time from swelling of 4.1±3.2 vs 3.1±2.9 years for PD1 vs PD≥2, p=0.031 and 4.5±3.4 vs 3.3±3.2 years for GS1 vs GS≥2, p≤0.0001).

Conclusions We conclude that subclinical joint activity is long-lasting in RA joints in clinical remission, but attenuates over time. The latter conclusion is based on the observed shorter time duration from last clinical activity for strong compared with weaker sonographic signals.

INTRODUCTION

Today's therapeutic targets in rheumatoid arthritis (RA) are remission or low-disease activity. The term remission is currently defined by the American College of Rheumatology and European League Against Rheumatism based on clinical and laboratory findings.[1 2] It has been suggested that subclinical inflammation can be detected in clinically inactive joints, especially by sonography.[3] Signs of synovitis, that is, synovial effusion and synovial hypertrophy, can be evaluated on grey scale (GS), while power Doppler (PD) techniques allow the sensitive characterisation of blood flow in small joints.[4] Sonography therefore seems to be highly suitable for the detection of subclinical synovitis in joints of patients with RA without clinical signs of activity.[5]

Further, sonographic synovitis has demonstrated predictive validity with regard to radiographic progression.[6] Stringent remission is associated with very low levels of PD signal, in contrast to less stringent remission definitions,[7] and clinical disease activity also corresponds to the grade of PD and GS signals, with higher grades predominantly shown in clinically active joints.[8] Thus, one could hypothesise that low-grade PD and GS signals in clinically inactive joints may constitute the remains of previously observed clinical activity in the respective joint after clinical signs have disappeared, and that these signs—if clinical joint remission is maintained—will also subside over time. Indeed, maintenance of stringent clinical remission is also associated with a complete halt of joint damage progression.[9]

In the present study, we investigated whether subclinical signs of activity decrease over time once clinical remission is reached and sustained.

METHODS

Patient selection and study outline

We recruited consecutive patients with RA with low-disease activity or remission from our outpatient clinic. All patients underwent sonographic assessment of 22 joints of the hands (bilateral proximal interphalangeal joints (PIPs), metacarpophalangeal joints (MCPs) and wrists).[8] All joints that showed positive sonographic findings but no signs of clinical swelling or tenderness by the time of sonographic assessment were selected for further analysis. We then identified all joints with documented swelling or tenderness at some point in the past (figure 1). We calculated the time that had elapsed between the last recorded clinical activity in a joint to the present sonographic (and clinical) assessment, and then related this time to the different sonographic grades. For further information about patient selection, clinical assessments, sonographic assessment, as well as radiological assessment and statistics, please see online supplementary text.

RESULTS

A total of 90 patients were included in this study with a majority of them (n=60; 66.7%) being in clinical remission as defined by Clinical disease activity index ≤2.8 at the time of the sonographic assessment, with the remainder having low-disease activity. Clinical and demographic data of all patients are shown in online supplementary table S1. Figure 1 depicts the further flow of the investigated joints. The sonographic findings in all joints that were clinically inactive at the time of the sonographic assessment are presented in online supplementary table S2. Online supplementary table S3 provides the sonographic findings separated by assessed joint region (wrist, MCP and PIP).

Endurance of subclinical joint activity on the joint level

The mean±SD time since last clinical swelling and positive sonographic assessment was significantly

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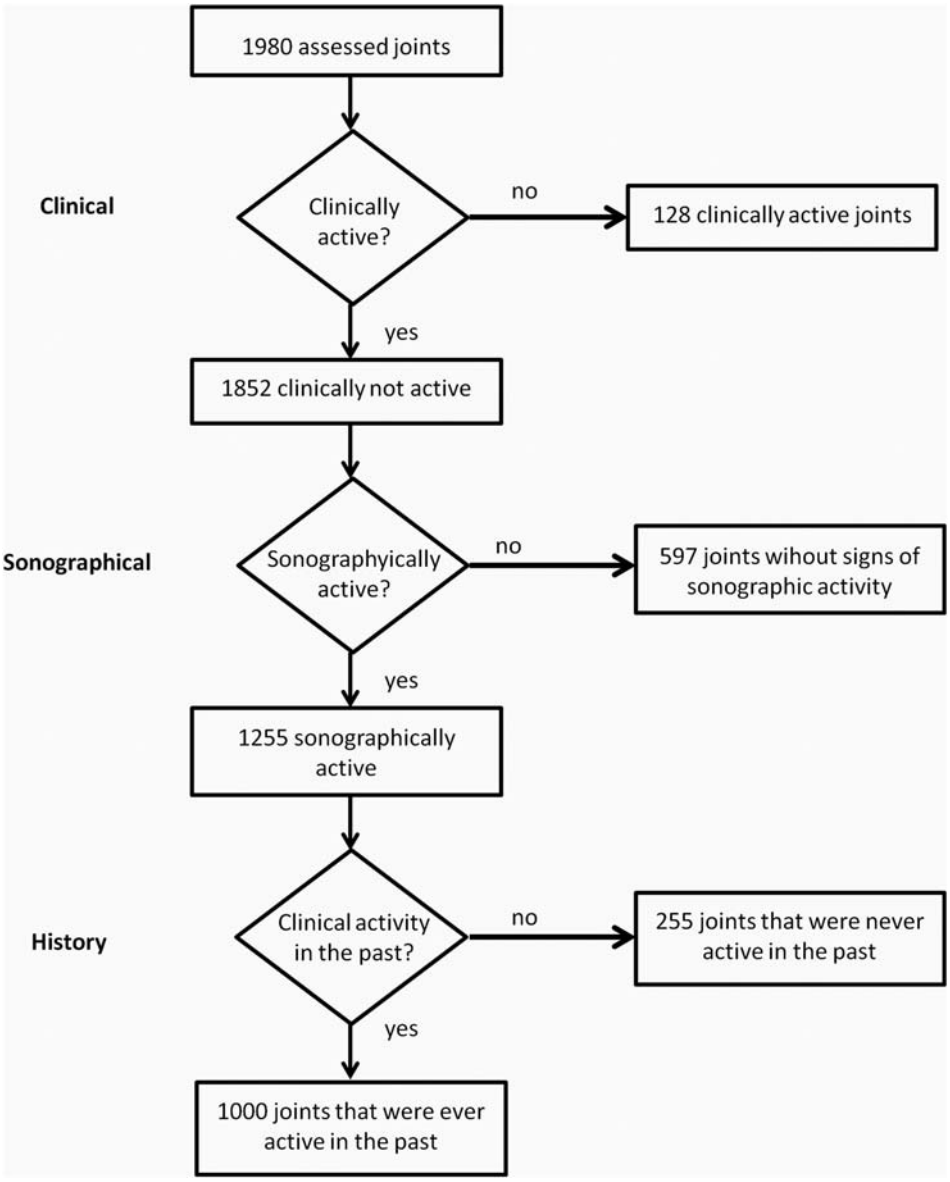

Figure 1 Flow chart of joint selection in all 90 patients. The starting points are all joints that are assessed clinically and by sonography.

shorter in joints showing higher GS signals compared with joints with lower-grade GS signals (4.5±3.4 years for GS=1; 3.7±3.3 years for GS=2 and 2.2±2.4 years for GS=3; p<0.001; figure 2A); considering grade 1 findings as potentially ambiguous and comparing them to unequivocal GS findings (grades 2+3), the times remained clearly significantly different (mean±SD time since last swelling: 4.5±3.4 vs 3.3±.2 years for GS1 vs GS≥2; p≤0.0001). For PD signals, although much less frequent in their overall occurrence, there was also a similar trend towards shorter periods of clinical joint remission in highly active joints (4.1±3.2 years for PD=1 vs 3.2±2.9 years for PD=2 and 1.6±2.1 years for PD=3; p=0.069; figure 2B); again comparing potentially ambiguous grade 1 findings with unequivocal grade 2+3 findings, the times averaged to 4.1±3.2 vs 3.1±2.9 years, respectively (p=0.031).

We also performed this analysis on the patient level; the respective data can be found in the online supplementary material.

Structural progression and the influence of osteoarthritis

Only a minority of joints showed progression in joint space narrowing (3.4%, n=34 joints) or in erosions (1.5%, n=15) at a mean duration from last swelling of 1.6±1.5 years.

Including osteoarthritis (OA) into our evaluation we found that joints with present osteophytes had significantly higher PD and GS levels (mean PD of 1.48±0.69 vs 1.28±0.47 and mean GS of 1.48±0.70 vs 1.28±0.56; p<0.0001 for both), but we found no significant difference in duration of subclinical joint activity in joints with or without radiographic evidence of osteophytes.

DISCUSSION

The results of our study support the notion that clinical joint remission may not denote the absence of inflammation. The data obtained clearly suggest decreasing frequencies and levels of detectable subclinical inflammation with increasing time in clinical remission. This latter finding is the most important insight revealed by the present study.

It might be regarded as logical that the continued absence of specific markers of inflammation (clinical swelling and/or tenderness) will lead to a progressively smaller number of joints with positivity for a sensitive marker (GS or PD on sonography). However, this connection has not been previously established over long periods of follow-up, probably because the prospective follow-up of a sufficiently large number of patients

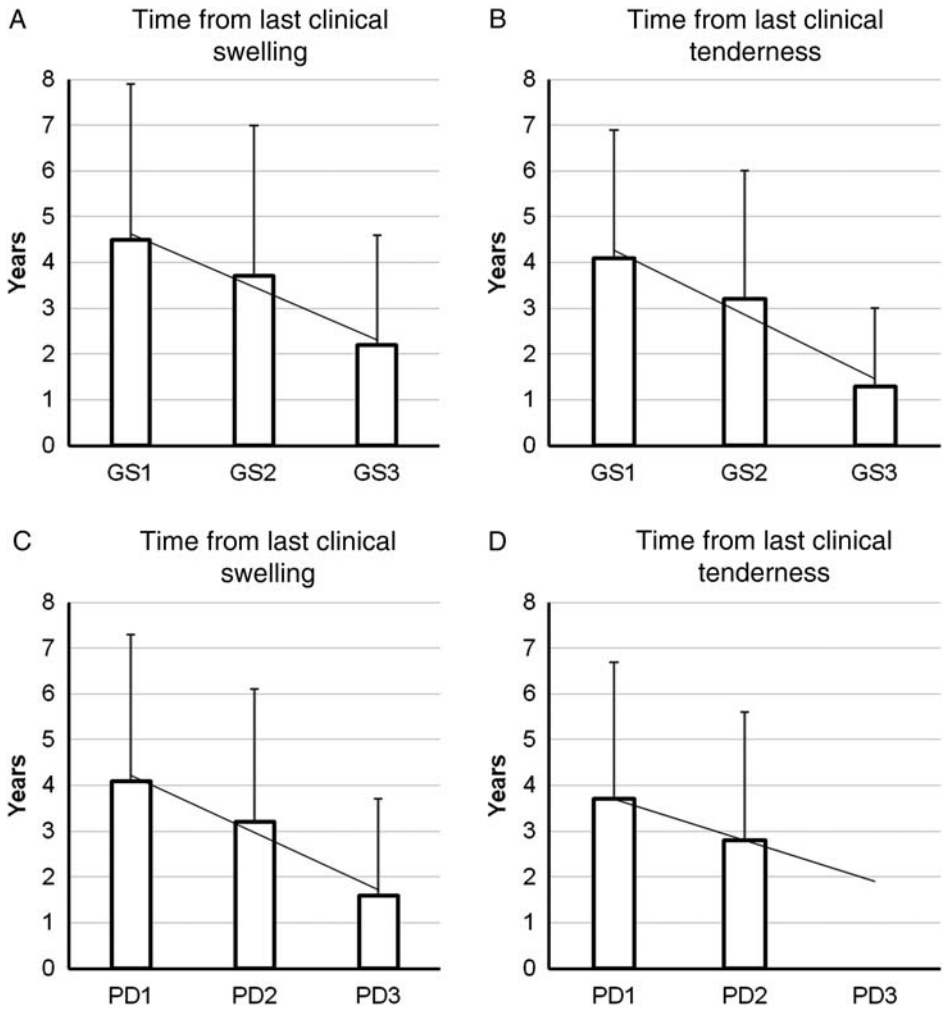

Figure 2 Time from last clinical activity (swelling or tenderness) for grey scale (GS; A) and power Doppler (PD; B) signals 1, 2 and 3. We found a significantly shorter period of clinical remission in joints showing high compared with low GS signals, and a similar trend for PD ($p<0.0001$ for GS and $p=0.069$ for PD).

who continue to have clinically inactive joints is not necessarily natural. Even less feasible would be to perform repeated sonographic examinations over a period of several years within the framework of a study. Such a study would still be the best way to address this question. Although the design of our study can be regarded as a possible limitation, it is doubtful—as a matter of feasibility—whether any long-term prospective evaluation will ever be performed to address this question.

In our study, we tried to overcome this difficulty by approaching the problem from the end and not the beginning, starting with the sonographic assessment of currently clinically inactive joints and tracking these joints back in time.

It is important to stress that the main objective here was not to determine the absolute time needed to remit to particular subclinical activity levels but to test the hypothesis that there would be a decrease of such levels with increasing time of clinical inactivity. Of course, there are several limitations of such an approach: first, we do not have any information on sonographic activity during the preceding years of clinical inactivity, and therefore cannot exclude that flares of subclinical activity (without clinical activity) occurred throughout the follow-up period; undetected clinical flares between visits are also possible, but this would also apply to any prospective study on outpatients. Second, while the main analysis is powerful by the number of joints, the data are not independent as multiple joints per patient are included. To overcome this problem, we looked in an additional analysis at the mean duration since last clinical activity across all joints of each single patient and aggregated these means across all patients. This overcomes the limitation of multiple observations per patient, while at the same time providing a robust estimate of the time from last clinical activity.

Based on the results of our study, namely that subclinical signs of activity seem to decrease over time spent in clinical remission, we can deduce that tight clinical control may be sufficient for monitoring disease activity in sustained remission. This tight clinical control, in accordance with the treat-to-target principle,[10] should eventually also lead to waning of subclinical activity. Further, we found that the presence of OA, as a possible confounder of our results, did not influence the time of subclinical joint activity. Also, we could show that subclinical signs of inflammation might not influence radiographic progression as only a small minority of joints showed any structural progression.

Our study confirms the value of sonography to detect the degree of subclinical disease activity since it may persist even over years in clinically inactive joints, and in particular to identify joints that have higher degrees of sonographic findings. Therapeutic implications may not necessarily be deduced from such findings as persistently maintained clinical remission will already have 'therapeutic' implications for the remaining subclinical findings.

In summary, sonography is a sensitive tool to understand the degree of inflammation in the joints of patients with RA. Its relative inexpensiveness and safety call for a wide use in RA, wherever feasible. In patients without any detectable clinical joint activity, sonographic assessment or other imaging techniques, such as MRI, may help localise the sites of such residual

subclinical activity. Nevertheless, before any additional diagnostic step is taken in a patient in clinical remission, or any therapeutic decision is made based on subclinical activity, the relatively benign structural implications thereof need to be factored in.

Contributors MG and FA: conception, design and data interpretation; data acquisition and analysis; drafting and final approval of the version to be published. GS and PM: data acquisition and analysis; drafting and final approval of the version to be published. JS and DA: conception, design and data interpretation; drafting and final approval of the version to be published.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was conducted according to the Declaration of Helsinki, approved by the local ethics committee.

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