Special Report

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Practical use of musculoskeletal ultrasonography in rheumatoid arthritis: how to use this attractive but arduous tool in clinical practice

Musculoskeletal ultrasonography (MSUS) is now commonly used by many rheumatologists in clinical practice, but much work is still required for its optimization. MSUS use in daily clinical practice should be feasible and practicable, at the same time, not redundant. MSUS should be used as a complementary procedure and not as an alternative to systematic clinical evaluation. MSUS can be minimally used on demand, at the point of care, to detect subclinical synovitis. Grading and scoring by ultrasonography in addition to clinical examination are not always required for the regular management of individual patient.

Keywords: clinical practice • grading • musculoskeletal ultrasonography • rheumatoid arthritis • scoring

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Musculoskeletal ultrasonography (MSUS) is now commonly used by many rheumatologists in clinical practice, but much work is still required for its optimization. Most rheumatologists, if not all, now understand the merit of MSUS. MSUS is noninvasive, cheap, immediately available (point of care MSUS), applicable to several articular sites, easy to repeat and, above all, suitable for dynamic studies. At the same time, as its demerits, it is pointed out that MSUS is operator-dependent and time consuming. Also, it has failed to demonstrate superior sensitivity to change as compared with clinical examination [1,2]. According to the recent ACR recommendation on the reasonable use of MSUS in rheumatology clinical practice [3], the use of MSUS is regarded as a complementary procedure rather than an alternative to clinical evaluation. The added value of sonographic assessment beyond clinical scoring and of its feasibility in routine clinical practice (availability of equipment and trained staff, time constraints, costs, *etc.*) are not confirmed [4]; so, much work is still required before replacing clinical examination to MSUS.

We should keep in mind that MSUS has two major roles in rheumatology:

- MSUS as a complementary procedure of clinical examination in clinical practice.
- MSUS as the objective reference standard in clinical trials.

The outcomes used in clinical trials is not always feasible in clinical practice. For example, most rheumatologists must be reluctant to calculate the total Sharp score of an established RA patient with severe joint deformity. Most rheumatologists judge the presence of progression of joint destruction by simply comparing two serial films.

Some serious rheumatologists misunderstand that they should use the same clinical outcomes in clinical practice as those used in clinical trials. Most clinical outcomes used in clinical trials such as DAS28 can also be applied in clinical practice. But some outcomes such as total Sharp score, are not always feasible in clinical practice. These important outcomes in clinical trials might not apply to individual patient care in clinical practice. Do we have to do MSUS of 28 joints for all RA patients at each visit? Do we need to grade the synovitis by MSUS or calculate the global synovitis score in clinical practice?

Future Medicine part of fsg

In this viewpoint, the problems in the evaluation of synovitis by MSUS in clinical practice will be discussed.

Detection of subclinical synovitis for early diagnosis

One of the most important purpose of MSUS in clinical practice is to detect subclinical synovitis. Rheumatologists who perform MSUS in clinical practice must have many experiences when the diagnosis of early RA was finally made with the findings of MSUS. In these cases, when no synovitis is detected by clinical examination, we cannot apply the 2010 ACR/EULAR classification criteria of RA. We should once again keep in mind that the classification criterion is different from diagnostic criteria [5]. In clinical practice, we can diagnose these patients as having early RA with the help of MSUS (Figure 1A & B). It is reported that MSUS assessment improves the accuracy of the 2010 ACR/EULAR criteria for identifying patients with a disease requiring MTX treatment [6]. On the other hand, one possible limitation of MSUS in the early diagnosis of RA is that subclinical synovitis detected with MSUS may include some false positive findings. There are numbers of reports that the sensitivity of MSUS for the detection of synovitis is better compared with clinical examination. But the problem is that there is no golden standard for the presence of synovitis. MSUS actually detects more synovitis but we should know that at least a part of subclinical synovitis detected by MSUS might not be clinically relevant, as higher sensitivity always results in lower specificity. It is reported that gray scale grade 1 findings are frequently observed in healthy control [7,8]. Another possible limitation is that, although we all know early diagnosis of RA is required for early treatment, at this moment, nobody knows if this slightly earlier diagnosis made with the help of MSUS would improve the long-term prognosis of these patients. With MSUS, we can diagnose RA early in patients without clinical synovitis before satisfying the RA classification criteria, possibly a few weeks earlier before these subclinical synovitis become clinically apparent synovitis when the window of opportunity may be still wide-open.

Detection of subclinical synovitis for assessment of disease activity in active RA

The next question is if MSUS add any clinically relevant value over routine clinical assessment in patients with active RA. In patients with active RA, the number of joints with synovitis is the sum of clinical synovitis and subclinical synovitis (Figure 1A). As long as there is a swollen joint detected with clinical examination, the treatment should be stepped up. At this point before clinical remission, extradetection of subclinical synovitis by MSUS would not result in the change of therapeutic strategy. As pointed out by Mandel, an instrument/variable should not be redundant, that is, not reflect an aspect of disease activity that another instrument/variable covers inherently [4]. Of course, MSUS might be useful to distinguish thickened joint with fibrotic scar tissue from swollen joint with active inflammation in longstanding RA. In my opinion, we do not always have to use MSUS to monitor disease activity in RA patients in clinical practice. A recent editorial even goes so far as to suggest the scanning of a single joint as a quick and simple MSUS measure of disease activity [9]. We may go further to scanning no joint in busy clinical practice.

Detection of subclinical synovitis for evaluating remission

There are numbers of studies that show the importance of MSUS in the evaluation of remission in RA (Figure 1C). In a met-analysis, it was confirmed that MSUS-detected residual synovitis is frequent and predicts the risk of relapse and structural progression in RA patients in clinical remission [10]. The problem is that, in these studies, the definition of clinical remission is not standardized. The most stringent definition might be the ACR/EULAR remission criteria. But, according to this criteria, a patient is considered to be in clinical remission even if he/she has one swollen joint. Thus, the predictive value of MSUS might include joints with clinical synovitis which often show moderate MSUS synovitis [11]. In fact, Gartner *et al.* concluded that low-grade PD and GS ultrasound signals in patients in clinical remission may not necessarily reflect the presence of active synovitis [12], and they assumed that low grade MSUS findings to be oversensitive. Another problem is that in most of the studies MSUS evaluation is done only at a single point in time. By this single point evaluation, we cannot distinguish the states of moderate synovitis that is recovering from severe synovitis from moderate synovitis newly appeared in a joint that was normal. These facts might explain the low positive predictive value of MSUS findings in the prediction of structural progression.

The fate of subclinical synovitis detected with MSUS

Figure 2 shows the hypothetical model of the fate of subclinical synovitis detected by MSUS. The fate of a subclinical synovitis may be classified as: rapid progressor; erosive synovitis; non-erosive synovitis; persistent subclinical synovitis; and self-limiting synovitis. Self-limiting synovitis may include false positive findings. We know that even a clinical synovitis does not always

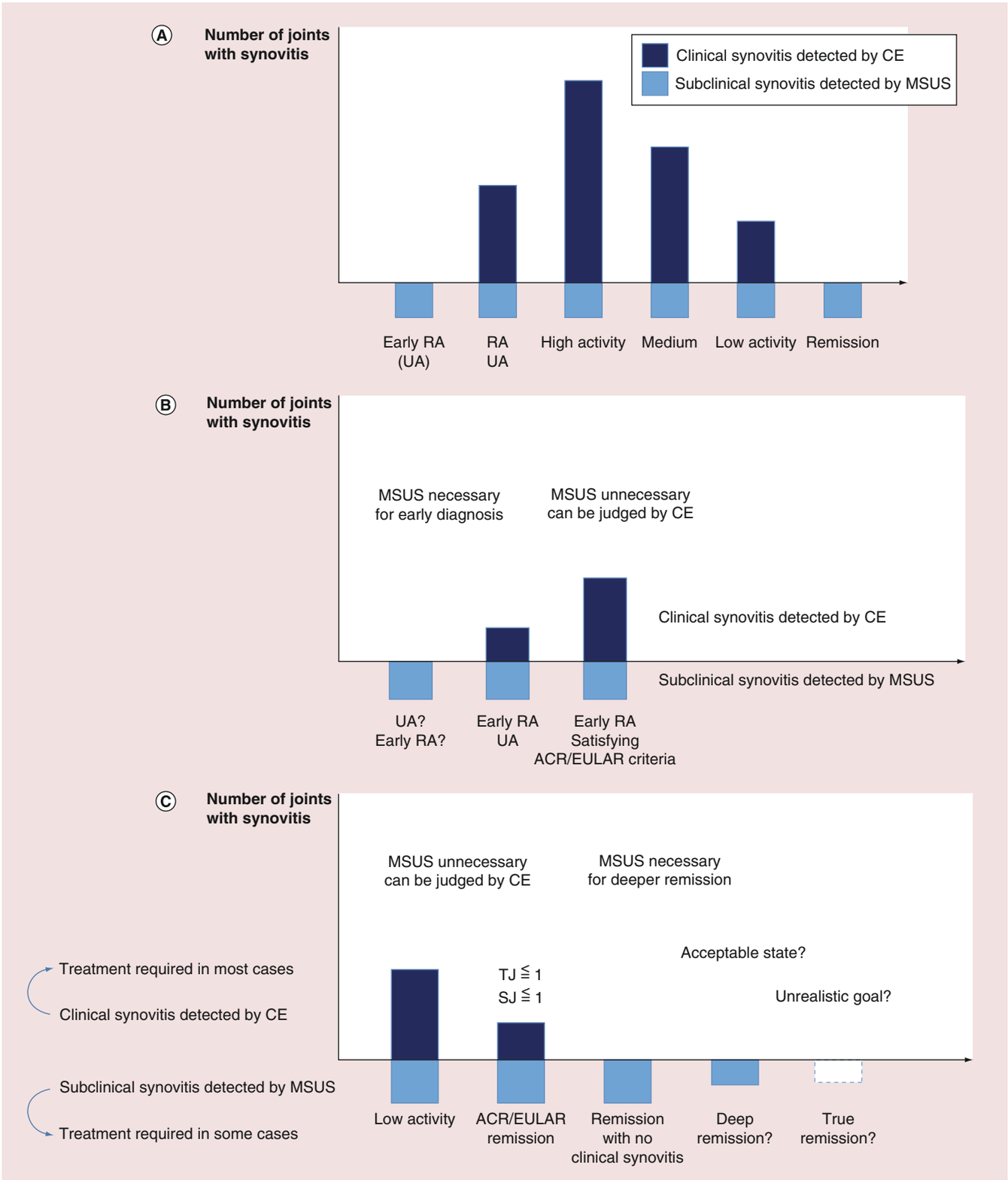

Figure 1. Numbers of joints with synovitis at different stages. (A) Progression of RA. **(B)** Onset of RA. **(C)** Remission of RA.
CE: Clinical examination; MSUS: Musculoskeletal ultrasonography; UA: Undifferentiated arthritis.

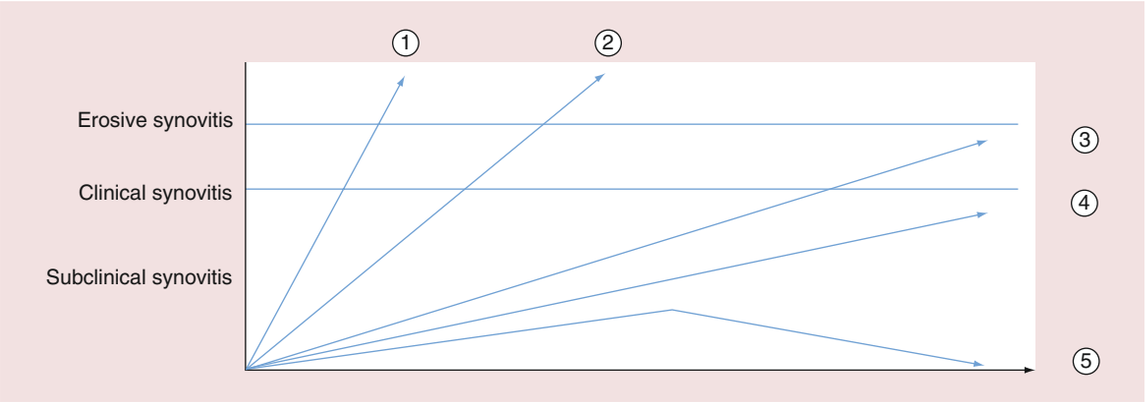

Figure 2. The fate of subclinical synovitis (hypothesis). (A) Rapid progressor; **(B)** erosive synovitis; **(C)** non-erosive synovitis; **(C)** persistent subclinical synovitis; **(D)** self-limiting synovitis.

result in erosive disease. Same might be true for subclinical synovitis. For instance, only 12 joints (5.8%) among 206 PD positive joints and 13 joints (3.7%) among 347 GS positive joints at baseline evaluation resulted in bone erosion after one year, respectively [13]. These strikingly low positive predictive values of MSUS findings may mean that most subclinical synovitis at a single point falls into either of non-erosive synovitis, persistent subclinical synovitis and self-limiting synovitis. So, under this hypothesis, subclinical synovitis is not considered as a therapeutic target but one of the risk factors of poor prognosis such as ACPA. MSUS imaging remission where there is no subclinical synovitis (Figure 1C) is not a realistic goal because subclinical synovitis is often observed in healthy controls and not all subclinical synovitis do not result in progression of erosion or clinical relapse. Therefore, trying to treat all subclinical synovitis might result in overtreatment. There is no method to distinguish erosive synovitis from non-erosive synovitis by MSUS.

Problems in MSUS grading

In the majority of recent MSUS studies, grading of synovitis is done according to the four grade semiquantitative system on a scale of 0–3 (grade 0 = none, grade 1 = mild, grade 2 = moderate, and grade 3 = severe), according to the Szkudlarek score [14]. Studies analyzing the inter- and intrarater variability of the above mentioned semiquantitative score have found moderate to good agreements. Agreements tend to be higher for the Doppler US score than for grey-scale US findings [15–20]. For grey-scale grading, as there is no clear definition of each severity that apply to all joints, the severity of synovitis is subjectively judged and there must be some overlaps between grades (Figure 3A & B). In addition, the present grading system of the joint is judged by the image of a single plane. In some studies, the image of the joint is acquired from a single midline aspect of the joint, while in others, the probe is swept across the joint to detect the most severe plane (Figure 3C). As the pathologies are always distributed heterogeneously within the joint, grading judged by the midline aspect of the joint sometimes results in underestimation. We know that synovitis in MCP2 or MCP3 is more common on the radial side, and that of MTP5 is more common on the lateral side. We may miss those pathologies unless we sweep the probe throughout the joint. In our pilot study, we observed that the assessment in the standard, longitudinal, dorsal-midline plane was far from an ideal method to evaluate the severity of the entire MCP2 joint [21]. So sonographers should not forget to thoroughly scan the joint to detect a wide range of MSUS pathologic features. Also, grading will easily change by subtle movement of the probe or adding extra-pressure with the probe. These are some of the reasons for inter- and intrarater variability in MSUS.

Another problem with the grading system is that the present grading system does not take into account the volume of the pathologies. It is the grade of a single plane of the joint but not the grade of the entire joint. For example, wrist joint with moderate synovitis throughout the entire radiocarpal, intercarpal and carpometacarpal joints is graded as grade 2, while the same wrist joint with severe synovitis only on a single CM joint is graded as grade 3 (Figure 4A). According to the present grading system, the latter could be judged to be more severe at least numerically, but clinically, the former may be more critical for the patient. It may be useful to express the volume of the pathologies, such as 'diffuse grade 2 synovitis' and 'focal grade 3 synovitis'.

Problems in MSUS scoring

In clinical trials, some global synovitis scoring systems are used. These scores are based on a concept of devel-

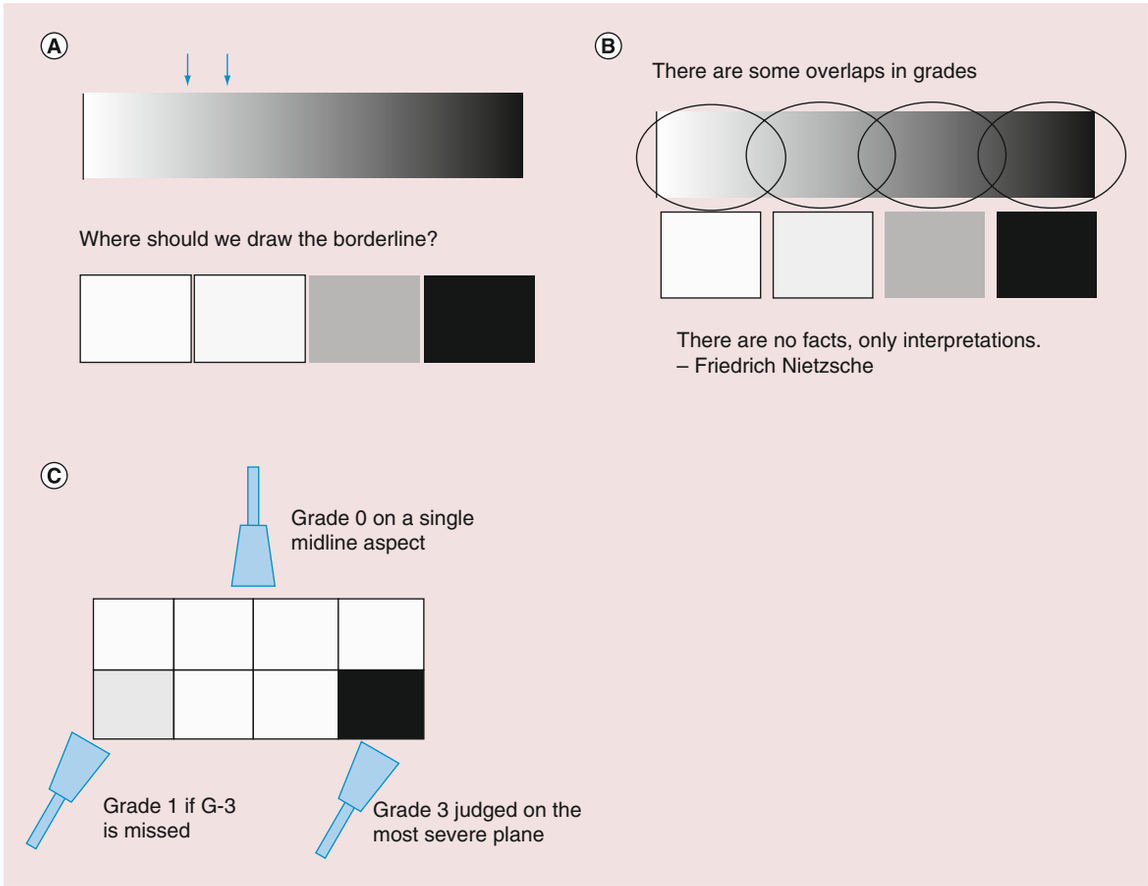

Figure 3. Problems in MSUS grading (1). (A) Semiquantitative grading: where should we draw the borderline? **(B)** Overlaps of grades. **(C)** Variability of grading due to different scanning planes. As the pathologic finding in a joint is heterogeneously distributed, the joint should be scanned entirely by multiple planes. If it is evaluated only on a single midline aspect, it would result in undergrading.

oping an MSUS scoring system for synovitis in RA at the patient level. Recent longitudinal studies applying either extensive or reduced MSUS joint counts have shown the feasibility of MSUS for following patients under treatment. However, many differences have been reported in the scoring system used. In a literature review, it was concluded that it is currently difficult to suggest a minimum number of joints to be included in a generally accepted global MSUS synovitis score [22]. These scoring systems, applied at the patient level by means of a multijoint MSUS assessment, might allow an objective followup of patients under treatment and should provide a feasible and objective instrument for evaluating disease activity in patients with RA. These scoring systems can be used mainly in clinical trials for the evaluation of patient group, but for clinical use in the evaluation of individual patient, there seems to be some problem. The current grading system applied at the joint level itself has some problem as mentioned above. Is it reasonable to sum these ambiguous grades of multiple different joints (Figure 4B)? Is it reasonable to compare the severity of individual patient with these scores?

Purpose of MSUS in clinical practice

There is no doubt that MSUS is an attractive tool for the evaluation of synovitis. There are many instances in which the evaluation of clinically swollen joint by ultrasound are useful in clinical practice. Showing the massive PD signal found in the swollen joint by MSUS helps RA patients to understand what is happening in their joint. Also it can result in the patients' decisions to accept more intensified expensive treatment. Patients are happy to see the improvement of the degree of PD signals with treatment. In patients with fibromyalgia, the absence of pathological findings shown by ultrasound can help patients to accept the disuse of DMARDs or corticosteroids. But much work is still required for its optimal use, especially in clinical practice. As stated in the ACR report, the use of MSUS should be viewed as a complementary procedure and not as an alternative to systematic clini-

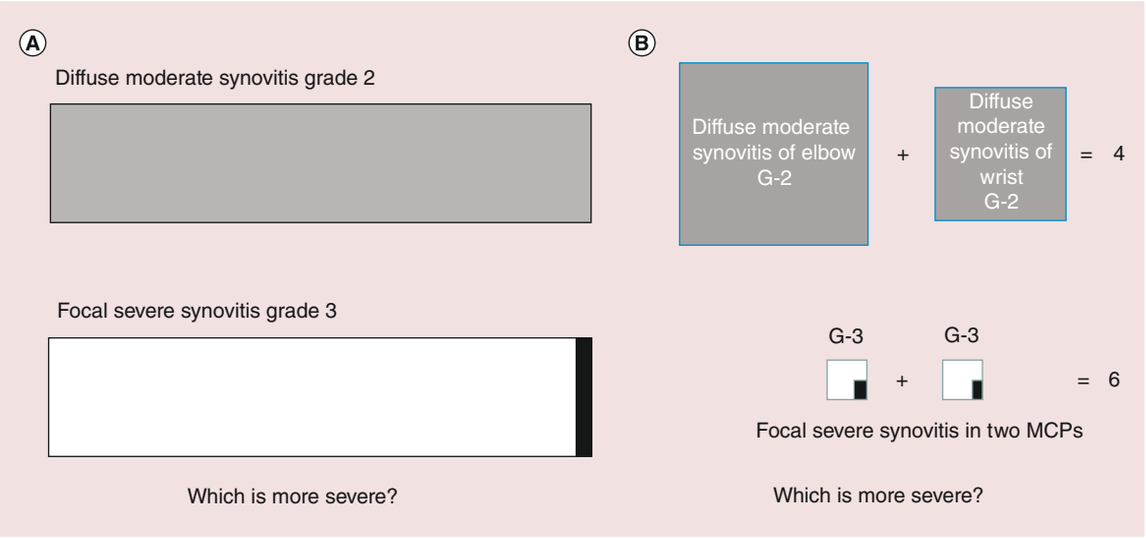

Figure 4. Problems in scoring using the present grading system.(A) Severity of grade: which is more severe? The clinical severity of the joint cannot be understood by the present grading system. The volume of the pathologies should be considered in clinical practice. **(B)** Global score: Mixing apples and oranges? The clinical severity of the patient cannot be understood by the present scoring system.

cal evaluation [3]. In none of the recommendations by ACR, the use of MSUS was not advocated when the clinical evaluation has already established the pathologies with a high level of confidence.

MSUS have added value to clinical examination to detect subclinical synovitis. In clinical practice, MSUS should be mainly used for patients with no clinical synovitis for its very high diagnostic and differential diagnostic value to diagnose early RA and confirm the state of remission. The evaluation of disease activities of patients with clinical synovitis, composite indices such as DAS, SDAI and CDAI which has shown high validity and sensitivity to change can be used. By this approach, MSUS becomes feasible enough for utilization in daily clinical practice for all rheumatologists.

Conclusion

We should not fall into an activity trap of performing MSUS. Sometimes, means become ends without realizing it. MSUS is one of a complementary tools to clinical evaluation to accomplish our goal of treating to target, and grading or scoring by MSUS are not the purpose by itself. MSUS can be minimally used on demand, at the point of care, to detect subclinical synovitis with thoroughly scanning the target joint. We should consider the volume and serial change of the pathology. Grading and scoring by ultrasonography in addition to clinical examination are not always required for the regular management of individual patient.

Future perspective

US joint scores with reduced joints such as US7 for clinical trials will be decided in the near future by leaders in this field. But such scores will not be appropriate for the care of individual patient in clinical practice. When scanning a joint according to the reduced joint score, a patient may point out, 'Doctor, it is not the joint I feel pain!' The doctor may say to a patient with active RA, 'You are in remission according to the reduced US joint score!' It is impossible to establish a reduced joint score which applies to every single patient in clinical practice. A tailor made evaluation is required.

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Executive summary

- It is possible to reasonably minimize the use of time-consuming MSUS in clinical practice.
- MSUS is a complementary procedure and not an alternative to clinical evaluation.
- Present grading systems and scoring systems used for clinical trials are not suitable for evaluation of individual patient in clinical practice.

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