Doctor, why does my hand hurt? The nature, course and treatment of pain in hand osteoarthritis

Meulen, C. van der

CHAPTER 8

SYNOVITIS SCORING IN HAND OSTEOARTHRITIS WITH ULTRASONOGRAPHY: THE PERFORMANCE OF THE GLOBAL OMERACT/EULAR ULTRASOUND SYNOVITIS SCORE (GLOESS) IS COMPARABLE TO SYNOVIAL THICKENING ALONE

Coen van der Meulen*, Marion C. Kortekaas*,
Maria Antonietta D'Agostino, Féline P.B. Kroon,
Frits R. Rosendaal, Margreet Kloppenburg
*CM and MCK contributed equally to this work.

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ABSTRACT

Background

Inflammation is increasingly recognized as a treatment target in hand osteoarthritis, and therefore correct measurement of local inflammation is essential. This study aimed to assess ultrasound scoring of synovitis and the additional value of the Global OMERACT/EULAR ultrasound synovitis score (GLOESS) in hand osteoarthritis.

Methods

Data from the randomized, double-blinded Hand Osteoarthritis Prednisolone Efficacy (HOPE) trial were used. The HOPE trial included patients with painful, inflammatory hand OA, treated with prednisolone or placebo (1:1). Ultrasound was performed in 30 hand joints at weeks 0, 6 and 14. Effusion, synovial thickening and Doppler signal were measured, the GLOESS was calculated from the latter two. Joint tenderness on palpation was assessed semi-quantatively (0-3), soft swelling as present/absent. Changes in ultrasound scores, and their association with change in joint tenderness or soft swelling, were investigated using generalized estimating equations. Effect sizes were calculated.

Results

Of 92 included patients 79% were women, with mean (SD) age 63.9 (8.8) and BMI 27.2 (4.6). Synovial thickening was the most prevalent. All ultrasound scores were strongly associated with joint tenderness and soft swelling cross-sectionally. There was no association of change in ultrasound scores with change in tenderness, but there was with change in soft tissue swelling. Synovial thickening and the GLOESS responded to treatment (effect size -0.39 (-0.72 to -0.07), -0.39 (-0.71 to -0.07), respectively).

Discussion

Various ultrasound scores were associated with joint tenderness and soft swelling. The GLOESS and synovial thickening were both responsive to treatment, but GLOESS was not superior to synovial thickening alone.

Key messages

What is already known on this topic

Inflammation is increasingly recognized as a treatment target in hand osteoarthritis, and therefore correct measurement of local inflammation is essential. Ultrasonography is often used to measure local inflammation in hand OA.

What this study adds

The Global OMERACT/EULAR ultrasound synovitis score (GLOESS) is responsive to anti-inflammatory treatment and is associated with joint tenderness. This is also seen for the individual feature synovial thickening. The GLOESS score showed no superiority over synovial thickening alone in measuring synovitis in hand OA.

How this study might affect research, practice or policy

Further exploration and investigation of the GLOESS system for use in patients with hand OA is warranted. Given the clear associations with pain and soft tissue swelling, synovitis measured with ultrasound remains of value in hand OA.

INTRODUCTION

Hand osteoarthritis (OA) is a prevalent disease that causes pain and loss of function, greatly impacting public health. (1) Unfortunately, treatment options are limited and disease modifying agents remain unavailable. Inflammation has been associated with both pain and structural damage, making it an important potential target for interventions. (2, 3) Recently, several randomized controlled trials showed promising results of anti-inflammatory agents such as prednisolone and methotrexate in hand OA. In these trials, effects on both pain and structural damage have been found, which shows that targeting inflammation can help in treating hand OA. (3-7)

The assessment of local inflammation in hand OA requires valid measurement tools, for which ultrasound is frequently used. The ultrasound scoring system for inflammatory features in hand OA has been shown to be both valid, reliable and feasible. (8-10) It also showed responsiveness in a recent trial comparing prednisolone to placebo, with differential decreases in synovial thickening between the intervention and placebo arms. This effect disappeared when medication was stopped. (4) Other ultrasound features such as effusion and Doppler signal did not show responsiveness, which suggests that not all features are equally responsive. Doppler signal has a lower prevalence compared to the other features, which may have affected the responsiveness.

In rheumatoid arthritis (RA), the OMERACT ultrasound working group has developed a composite score consisting of the individual ultrasound features synovial hypertrophy and Doppler signal: the Global OMERACT/EULAR ultrasound synovitis score (GLOESS). (11) The combined score showed good responsiveness to change after initiation of therapy even after 1 week in a cohort of rheumatoid arthritis patients, as well as in psoriatic arthritis (PsA) patients against placebo. (12-14)

Considering the need for precise measurement tools for inflammation in hand OA and the findings of good performance of the GLOESS in both RA and PsA, it was hypothesized that the score could be of added value in hand OA trials. Therefore, the aim of the present study was to investigate the performance of the different individual ultrasonography features in inflammatory hand OA (effusion, synovial hypertrophy and Doppler signal) compared to the performance of the combined GLOESS.

METHODS

Study design

Data from the Hand Osteoarthritis Prednisolone Efficacy (HOPE) study, a double-blind, randomized, placebo-controlled trial, were used. Full details and the protocol were published earlier. (4) The study received approval by the medical ethics committees at the Leiden University Medical Center (LUMC) and Zuyderland medical center (approval number P15.096). All patients provided written informed consent.

Study population

The HOPE study included adults with symptomatic hand OA following the ACR criteria. (15) Furthermore, eligible patients were required to have signs of inflammation (≥1 distal interphalangeal joint (DIP)/proximal interphalangeal joint (PIP) with soft swelling or erythema, ≥1 PIP/DIP with a positive Doppler signal or ≥1 PIP/DIP with synovial thickening of grade ≥2 on ultrasound investigation of digits 2-5) and finger pain of ≥30mm on a 100mm visual analog scale (VAS) with a flare-up after washout of non-steroidal anti-inflammatory drugs (NSAIDs). The flare-up criterium was amended due to slow accrual during the trial, so that patients without a flare-up but who fulfilled all other inclusion criteria and fulfilled a more stringent pain (VAS ≥40mm) and ultrasound (positive Doppler signal) criterion were also included.

Exclusion criteria consisted of pain predominantly located in the thumb base rather than fingers; presence of fibromyalgia or chronic inflammatory rheumatic disease, or seropositivity for rheumatoid factor or anti-cyclic citrullinated protein antibodies as well as safety concerns. Finally, patients who used systemic or local immunomodulating drugs including corticosteroid injections or received hyaluronic acid injections in the thumb base up to 90 days before start of the trial were excluded. (4)

Randomization, blinding and intervention

Patients were randomly (1:1) assigned to receive either prednisolone or placebo (identical in appearance, smell and taste) using a block randomization scheme with a fixed

block size of six. Prednisolone and placebo were self-administered in a dose of 10 mg per day for 6 weeks, after which medication was tapered to cessation in two weeks. Paracetamol (as rescue) and a stable dosage of chondroitin sulphate, glucosamine, bisphosphonate, tetracycline, or estrogens were allowed. NSAIDs and injections with glucocorticoids or hyaluronic acid, intramuscular or intra-articular, at any location, were not allowed. Patients were advised against starting non-pharmacological interventions during the trial.

Patients, outcome assessors and data analysts remained blinded for treatment allocation until the database was locked.

Ultrasound outcomes

Ultrasound was performed at baseline, week 6 and week 14 by two ultrasonographers (MCK, FPBK), in consensus. During ultrasound, synovial thickening, Doppler signal and effusion were assessed and scored semi-quantitatively (0-3 per joint in the DIP, PIP, MCP and CMC-1 joints) (16). Scans were performed on the dorsal side, longitudinal plane, using the transverse plane to confirm findings as needed. Synovial thickening and Doppler signal scores were then used to calculate the GLOESS score as described in the original publication and in appendix 1. (11) The GLOESS score is always at least equal to the synovial thickening score. In case of missing data for Doppler signal score, we thus determined the GLOESS to be equal to the synovial thickening. This was the case for the joints of one patient at week 6. In case of missing synovial thickening score, the GLOESS was determined to be missing for that joint. For an overview of the scoring see appendix 1.

Ultrasound features were summarized on the patient level by calculating sum scores for the individual features (synovial thickening, Doppler signal and effusion) and the GLOESS score. If all joints for a single patient had missing scores, the sum score was regarded as missing. When at least one joint was available a sum score was calculated for the available joints. Most participants (82) had complete data for all joints. At baseline, four patients missed data on a single joint (for one of whom ultrasonography was possible at weeks 6 and 14), three missed data on two joints, two missed data on three joints, and one missed data on seven joints. For the separate features, missingness was due to previous surgery or an anatomical deformity of the joint and thus stable over the visits. Some joints (3 at baseline, 2 at week 6 and 4 at week 14) had a Doppler score >0 but a synovial thickening score of 0. As the GLOESS does not allow for these combinations, these joints were determined to have missing GLOESS scores. Furthermore, 6 patients had dropped out during the study at week 6, with an additional 2 dropped out at week 14, as described in the original publication. (4)

The majority of ultrasound scans were performed at the LUMC (MCK, FPBK), with a minority performed at the Zuyderland Medical Center (FPBK). All patients were followed by the same sonographer during participation. Ultrasound was performed using a GE Logiq E9 (GE Healthcare, Chicago, Illinois, United States) with a 6-15 MHz linear array transducer in the LUMC, and with a Siemens Acuson NX3 Elite (Siemens Healthineers, Erlangen, Germany) with a 5-16 MHz linear array transducer in the Zuyderland Medical Center. Both machines were optimized by the application specialist at the start of the study and kept constant. An atlas with examples was used to facilitate reliable scoring (ISBN/EAN 978-90-827311-0-1).

Static images of 10 randomly selected patients were scored in consensus again to assess reliability. Single measure intra-class correlations were calculated on joint level (mixed effects model, absolute agreement) for both synovial thickening (ICC 0.71, 95% confidence interval [CI] 0.65-0.76) and Doppler signal (ICC 0.94, 95% CI 0.92-0.95). MCK previously demonstrated a high reliability for scoring effusion on ultrasound (ICC 0.73). (9)

Other outcomes

At baseline, clinical information of patients was collected through physical examination and questionnaires. Questionnaires included demographics (age, sex), visual analogue scales (VAS) for pain in the fingers and the Australian/Canadian Hand Osteoarthritis Index (AUSCAN). (17) Through physical examination, joint tenderness was collected for the first IP, DIP, PIP, MCP and CMC-1 joints semi-quantitatively (0-3), soft tissue swelling was collected as present/absent for the same joints.

Posterior-anterior radiographs were obtained at baseline or within 6 months before start of the study and scored following the Kellgren-Lawrence system (0-4 per joint, total score 0-120). (18) Erosive OA was scored according to the Verbruggen-Veys system. (19) Reliability of scoring was good. (4)

Statistical analysis

Population characteristics were described using mean (standard deviation) or median (interquartile range) for continuous variables, depending on normality of the data, or using n (%) for categorical variables.

Cross-sectional associations of ultrasound scores with joint tenderness were assessed by dichotomizing joint tenderness from a 0-3 score to a 0/1 score, with 0 indicating no tenderness (original score 0) and 1 encompassing various degrees of joint tenderness (original scores 1, 2 and 3). Association of ultrasound scores with the presence of joint

tenderness was then assessed with logistic Generalized Estimating Equations (GEE), with robust standard errors and the correlation structure specified as exchangeable. Joint tenderness was the dependent variable, ultrasound scores were the independent variable, with an ultrasound score of 0 as the index group. The models were first run without adjustment, and then adjusted for age, sex and BMI. Soft tissue swelling, collected as being present or absent per joint, was analyzed in the same way as joint tenderness.

Development of ultrasound scores over time up to week 14, dependent on treatment (placebo vs prednisolone), was analyzed using gaussian GEE, with robust standard errors and the correlation structure specified as exchangeable. Separate models were specified for effusion, synovial thickening, Doppler signal and GLOESS scores adjusted for treatment, center and baseline ultrasound scores. An interaction term between treatment and time was added to investigate the treatment effect at different follow-up timepoints.

To better compare the different ultrasound scores (specifically, synovial thickening to GLOESS), we estimated effect sizes, calculated by dividing the estimate from the GEE models by the SD of the ultrasound score at baseline for the whole group.

To assess the association of changes in ultrasound features and changes in joint tenderness we categorized the individual joints as having decreased or not having decreased (i.e. remaining stable or increasing) in pain and the ultrasound feature from baseline to week 6. Joints had to be able to show a decrease in both pain and the ultrasound feature investigated for this analysis, so joints with a pain score of 0 or an ultrasound score of 0 for the investigated feature were removed from the analysis.

To assess the association of increase in ultrasound features with increase in pain, we applied a similar approach. Joints were categorized as either having increased in pain or the ultrasound feature, or as not having increased (remaining stable of decreasing). Joints had to be able to increase, so joints with the maximum score of 3 for either pain or the ultrasound feature were excluded.

Associations for changes over time were then assessed using logistic GEE models, with robust standard errors, the correlation structure specified as exchangeable, with change in tenderness as dependent and change in ultrasound feature as independent. The models were first run without adjustment, and then adjusted for age, sex and BMI. Finally, the models were adjusted for treatment group.

This approach was also used to analyze associations of changes in ultrasound features and changes in soft swelling. Ultrasound features were categorized the same way they were for the analysis with tenderness. Change in soft swelling was categorized as an increase when a joint developed new soft swelling during follow-up (incident soft swelling) in joints at baseline without soft swelling, and categorized as a decrease when a soft swelling was seen in a joint at baseline but not at follow-up (disappearance of soft swelling). Associations with change in ultrasound features were analyzed using logistic GEE models, in an identical method as used for tenderness.

Analyses were performed using Stata version 16.1 (Statacorp).

RESULTS

Population demographics

The HOPE study included 92 patients, 46 (50%) in the placebo group and 46 (50%) in the prednisolone group. The population consisted of 79% women, with a mean (SD) age of 63.9 (8.8) and mean (SD) BMI of 27.2 (4.6). The median Kellgren-Lawrence sum score was 38, with interquartile range 28.5-46.5. Mean (SD) VAS pain in the fingers was 54 (20.5). Erosive disease was present in 67 (73%) of patients. The treatment groups were similar at baseline (appendix 2).

Baseline ultrasound scores

Average baseline sum scores for the US scores are shown in table 1. The proportion of patients with US features was similar between treatment groups. Synovial thickening was the feature with the highest mean score, followed by effusion and then by Doppler signal. The mean GLOESS score was higher than any individual score (table 1). For all ultrasound features, a score of 1 was the most prevalent, occurring more than twice as often as the scores of 2 and 3 combined. The exception was the Doppler signal, for which higher scores were relatively more prevalent. The PIP joints were the joints with the highest prevalence of most features, except effusion, which was most prevalent in the first IP joints. The MCP joints had the lowest prevalence of inflammatory ultrasound features (appendix 3). All ultrasound markers were strongly and dose-dependently associated with joint tenderness in cross-sectional analysis (table 2). Effusion showed dose-dependency for scores 0-2, but the effect attenuated for score 3. Strong associations between ultrasound features and soft joint swelling were also found (table 2).

Table 1. Baseline values of ultrasound scores

	Mean (SD)		
	Total (n=92)	**Prednisolone (n=46)**	**Placebo (n=46)**
Synovial thickening (0-90)[1]	17.1 (6.3)	16.4 (6.3)	17.8 (6.3)
Doppler signal (0-90)[2]	6.2 (4.3)	5.3 (4.1)	7.0 (4.3)
Effusion (0-90)[3]	12.2 (6.7)	12.2 (6.8)	12.2 (6.6)
GLOESS (0-90)[4]	17.8 (6.4)	17.0 (6.5)	18.6 (6.3)

Data presented as mean (SD). 1. N=19 missing joints. 2. N=19 missing joints. 3. N=20 missing joints. 4. N=23 missing joints. Some data contained in this table was previously published in the original analysis of the HOPE trial. (4)

Table 2. Cross-sectional association of ultrasound markers with soft joint swelling and tenderness

	Tender joints; N (%)	**Odds ratio (95% CI)**	**Soft swollen joints; N (%)**	**Odds ratio (95% CI)**
Effusion				
0 (n=1953)	273 (14.0)	1	176 (9.0)	1
1 (n=527)	117 (22.2)	1.80 (1.44-2.26)	99 (18.8)	2.36 (1.76-3.17)
2 (n=187)	88 (47.1)	5.23 (3.73-7.34)	58 (31.0)	4.43 (3.22-6.10)
3 (n=73)	30 (41.1)	3.55 (1.96-6.43)	27 (37.0)	5.71 (3.39-9.60)
Doppler signal				
0 (n=2405)	353 (14.7)	1	225 (9.4)	1
1 (n=160)	61 (38.1)	4.04 (2.83-5.77)	44 (27.5)	3.66 (2.27-5.94)
2 (n=119)	56 (47.1)	6.30 (4.49-8.84)	49 (41.2)	7.23 (4.48-11.67)
3 (n=57)	39 (68.4)	11.92 (7.10-20.01)	43 (75.4)	30.55 (16.84-55.42)
Synovial thickening				
0 (n=1591)	171 (10.8)	1	96 (6.0)	1
1 (n=805)	186 (23.1)	2.68 (2.11-3.43)	122 (15.2)	2.74 (1.95-3.83)
2 (n=269)	110 (40.9)	6.52 (4.83-8.80)	93 (34.6)	8.50 (5.70-12.66)
3 (n=76)	42 (55.3)	12.30 (7.40-20.43)	50 (65.8)	33.22 (18.94-58.28)
GLOESS				
0 (n=1587)	171 (10.8)	1	96 (6.1)	1
1 (n=766)	166 (21.7)	2.47 (1.92-3.17)	106 (13.8)	2.44 (1.71-3.49)
2 (n=280)	110 (39.3)	6.15 (4.61-8.21)	90 (32.1)	7.54 (5.02-11.31)
3 (n=104)	62 (59.6)	13.67 (8.82-21.17)	69 (66.4)	32.52 (20.12-52.57)

Score of 0 as index for each ultrasound marker. Analyses adjusted for age, sex, body mass index and clustering of joints within patients. CI = Confidence interval

Comparison of ultrasound features

Of the individual ultrasound features, only synovial thickening showed a response to prednisolone, seen as a difference between the treatment groups over time (between group difference -2.48, 95% CI -4.51 to -0.45 at week 6, as published previously (4)). No effects were seen for Doppler and effusion scores. The GLOESS score showed a between group difference of -2.50 (95% CI -4.58 to -0.43) at week 6. Associated effect sizes, calculated using the baseline SD of the ultrasound features, were -0.39 for synovial thickening and -0.39 for the GLOESS score (table 3). Effects attenuated after cessation of medication, as seen by the convergence of lines for all ultrasonographic scores in figure 1.

Table 3. Change in ultrasound scores over study period

	Mean between group difference at week 6	SD at baseline	Effect size
Synovial thickening	-2.48 (-4.51 to -0.45)	6.3	-0.39 (-0.72 to -0.07)
Doppler signal	-0.40 (-2.18 to 1.37)	4.3	-0.09 (-0.51 to 0.32)
Effusion	0.87 (-0.91 to 2.64)	6.7	0.13 (-0.14 to 0.39)
GLOESS	-2.50 (-4.58 to -0.43)	6.4	-0.39 (-0.71 to -0.07)

Comparison of change in ultrasound scores over 6 weeks, adjusted for baseline values and study center. Mean between group difference derived from GEE models, and subsequently transformed to effect sizes using baseline SD. Some of the data in this table was previously published in the original analysis of the HOPE trial. (4)

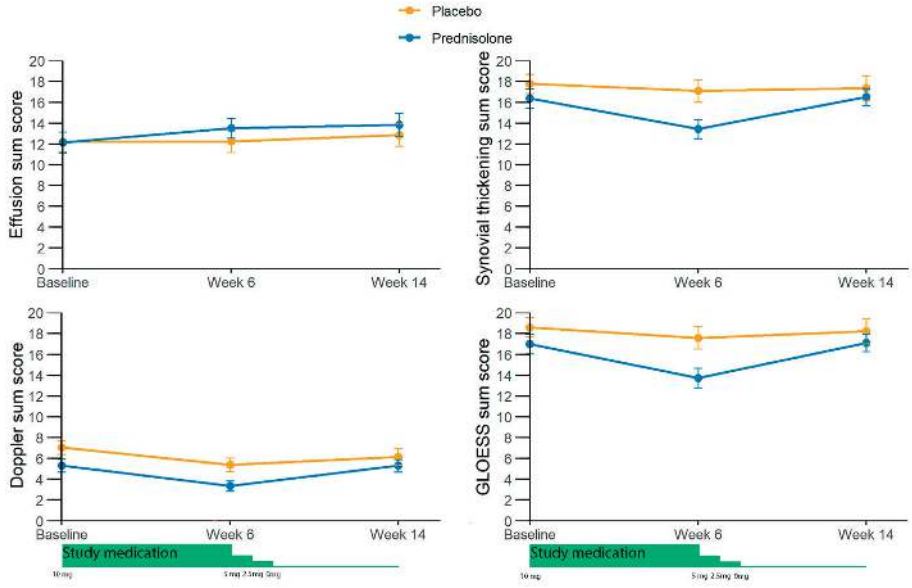

Figure 1. Changes in ultrasound scores over time

Changes of effusion, synovial thickening, Doppler and GLOESS sum scores over 14 weeks of follow-up. Yellow lines indicate placebo group, blue lines indicate prednisolone group. Data shown as mean ± standard error. Some data in the figure was previously published in the original analysis of the HOPE trial. (4) GLOESS = Global OMERACT/EULAR Ultrasound Synovitis Score.

Changes in ultrasound features did not show an association with change in joint tenderness over 6 weeks, for either an increase or a decrease (tables 4 and 5). These results did not change with adjustment for age, sex and BMI. Associations were seen between increase in Doppler, synovial thickening and GLOESS scores and incident soft swelling, but not for increase in effusion. An association was also seen for decrease in Doppler score and disappearance of soft swelling, but not for the other ultrasound features. Adjustment for age, sex and BMI did not change these results.

Table 4. Associations of increase in pain with increase in ultrasound features on the joint level in joints with pain and US scores of at most 2

	N joint with increased pain/total joints (%)	Odds ratio (95% confidence interval)		
Effusion		**Model 1**	**Model 2**	**Model 3**
Stable/decrease	125/2101 (6.0)			
Increase	32/353 (9.1)	1.32 (0.86-2.04)	1.32 (0.86-2.04)	1.36 (0.87-2.11)
Doppler signal				
Stable/decrease	140/2349 (6.0)			
Increase	11/98 (11.2)	1.71 (0.77-3.82)	1.71 (0.77-3.81)	1.70 (0.79-3.67)
Synovial thickening				
Stable/decrease	131/2142 (6.1)			
Increase	24/311 (7.7)	1.10 (0.67-1.81)	1.10 (0.67-1.81)	1.10 (0.67-1.78)
GLOESS				
Stable/decrease	125/2117 (5.9)			
Increase	24/309 (7.8)	1.15 (0.73-1.81)	1.15 (0.73-1.80)	1.15 (0.74-1.78)

Only joints with US and pain scores of 0/1/2 included, as increases is not possible for joints with a score of 3. Model 1: Analyses adjusted for clustering of joints within patients. Model 2: Analyses adjusted for age, sex, body mass index and clustering of joints within patients. Model 3: Analyses adjusted for age, sex, body mass index, treatment group and clustering of joints within patients.

Table 5. Associations of decrease in pain with increase in ultrasound features on the joint level in joints with pain and US scores of at least 1

	N joints with decreased pain/total joints (%)	Odds ratio (95% confidence interval)		
Effusion		**Model 1**	**Model 2**	**Model 3**
Stable/increase	85/130 (65.4)			
Decrease	42/67 (62.7)	0.92 (0.42-2.01)	0.93 (0.42-2.06)	0.93 (0.42-2.08)
Doppler signal				
Stable/increase	29/53 (54.7)			
Decrease	55/83 (66.3)	1.62 (0.82-3.21)	1.59 (0.79-3.20)	1.42 (0.69-2.95)
Synovial thickening				
Stable/increase	128/196 (65.3)			
Decrease	68/98 (69.4)	1.05 (0.59-1.87)	1.06 (0.59-1.89)	1.00 (0.54-1.87)
GLOESS				
Stable/increase	126/189 (66.7)			
Decrease	70/104 (67.3)	0.89 (0.51-1.56)	0.90 (0.51-1.57)	0.85 (0.47-1.54)

Only joints with US and pain scores of 1/2/3 included, as decreases is not possible for joints with a score of 0. Model 1: Analyses adjusted for clustering of joints within patients. Model 2: Analyses adjusted for age, sex, body mass index and clustering of joints within patients. Model 3: Analyses adjusted for age, sex, body mass index, treatment group and clustering of joints within patients.

Table 6. Associations of incident soft tissue swelling with increase in ultrasound features on the joint level in joints without soft tissue swelling at baseline

	N joint with increased soft swelling/total joints (%)	Odds ratio (95% confidence interval)		
Effusion		**Model 1**	**Model 2**	**Model 3**
Stable/decrease	79/2134 (3.7)			
Increase	18/359 (5.0)	1.46 (0.85-2.52)	1.46 (0.84-2.52)	1.46 (0.85-2.53)
Doppler signal				
Stable/decrease	89/2124 (4.2)			
Increase	12/72 (16.7)	4.15 (1.94-8.89)	4.42 (2.00-9.76)	4.37 (1.98-9.66)
Synovial thickening				
Stable/decrease	76/1939 (3.9)			
Increase	21/271 (7.8)	1.98 (1.14-3.43)	2.04 (1.17-3.55)	2.03 (1.17-3.52)
GLOESS				
Stable/decrease	73/1925 (3.8)			
Increase	19/273 (7.0)	1.84 (1.04-3.28)	1.91 (1.06-3.41)	1.89 (1.06-3.37)

Only joints with US of 0/1/2 included, as increases is not possible for joints with a score of 3. Only joints without soft swelling at baseline included, as incident swelling is only possible in those joints. Model 1: Analyses adjusted for clustering of joints within patients. Model 2: Analyses adjusted for age, sex, body mass index and clustering of joints within patients. Model 3: Analyses adjusted for age, sex, body mass index, treatment group and clustering of joints within patients.

Table 7. Associations of disappearance of soft tissue swelling with decrease in ultrasound features on the joint level in joints with soft tissue swelling at baseline

	N joints with decreased soft swelling/total joints (%)	Odds ratio (95% confidence interval)		
Effusion		**Model 1**	**Model 2**	**Model 3**
Stable/increase	55/104 (52.9)			
Decrease	29/54 (53.7)	0.95 (0.46-1.94)	0.97 (0.46-2.03)	0.97 (0.47-2.04)
Doppler signal				
Stable/increase	12/56 (21.4)			
Decrease	34/67 (50.8)	3.29 (1.44-7.52)	3.53 (1.51-8.26)	3.53 (1.49-8.37)
Synovial thickening				
Stable/increase	85/159 (53.5)			
Decrease	51/82 (62.2)	1.37 (0.77-2.42)	1.38 (0.78-2.46)	1.33 (0.74-2.41)
GLOESS				
Stable/increase	82/153 (53.6)			
Decrease	54/88 (61.4)	1.29 (0.75-2.21)	1.30 (0.75-2.25)	1.27 (0.73-2.21)

Only joints with US scores of 1/2/3 included, as decreases is not possible for joints with a score of 0. Only joints with soft swelling included, as disappearance of swelling is not possible otherwise. Model 1: Analyses adjusted for clustering of joints within patients. Model 2: Analyses adjusted for age, sex, body mass index and clustering of joints within patients. Model 3: Analyses adjusted for age, sex, body mass index, treatment group and clustering of joints within patients.

DISCUSSION

We studied the performance of the GLOESS compared with separate inflammatory ultrasound features in hand OA by assessing responsiveness and associations with the clinical outcomes joint tenderness and soft tissue swelling in a trial population with inflammatory hand OA treated with prednisolone versus placebo over 6 weeks.

Responsiveness was shown for the GLOESS and synovial thickening scores, without obvious difference between them, while no responsiveness was seen for Doppler signal and effusion. These findings are in line with previous studies describing the GLOESS to be responsive to change in RA, PsA, and gout. (12-14, 20) When compared to Doppler and synovial thickening scores, no clear increased responsiveness of the GLOESS was found in these studies either. (12-14, 20) Similarly, in our study, responsiveness of the GLOESS closely mirrored the responsiveness of synovial thickening score. This suggests that the synovial thickening score is the primary driver of the GLOESS score in hand OA, which may be due to the low prevalence of Doppler signal compared to synovial thickening (12% vs 42%). This may be different for conditions other than hand OA, where Doppler signal is more prevalent.

The low prevalence of Doppler signal positive joints in hand OA could also explain the overall lack of a between-group effect in change in Doppler signal, as was seen for synovial thickening and GLOESS scores. Another hypothesis is that Doppler may require more time to respond to treatment than six weeks. This cannot be determined based on the current data.

The associations of ultrasound features and clinical markers (tender and swollen hand joints) were assessed to further investigate the performance of the GLOESS score. All ultrasound scores were strongly associated with joint tenderness in cross-sectional analysis, with clear dose-response effects, similar to previous findings. (9) Even stronger associations were seen for soft tissue swelling. No clear benefit of the GLOESS score over synovial thickening as a separate feature was found.

Of interest were the associations between tenderness and effusion, where associations grew stronger from scores 1 to 2, but attenuated for scores of 3. It has previously been suggested that effusion might have an inverse effect on the osteoarthritic joint compared to other inflammatory markers. (21) This finding adds further credence to this hypothesis, although confirmation is still required. The stronger associations seen with soft swelling may be due to the more objective nature of swelling compared to tenderness. Also, the multifactorial etiology of pain might play a role. (22)

No significant association of change in ultrasound inflammatory features and clinical outcomes over time was found in this study for joint tenderness. Similarly, previous work on the GLOESS score in RA showed that the association between response in GLOESS and response in the disease activity score 28 was almost completely absent. (23) Previous studies in hand OA are lacking. In hand OA an association between presence of inflammatory US features at baseline and pain three months later was found, but change of US features over time were not assessed. (24)

In this study, we found no association between change in tenderness and change in ultrasound scores. The lack of association between change in joint tenderness and change in the ultrasound scores in this study may be due to various reasons. In the current analysis of trial data, the placebo effect may lead to decreased reported tenderness without structural changes. Furthermore, prednisolone intake in half our population may have affected more than just inflammation, for example mood. (25) This in turn can affect reported tenderness due to the multifactorial nature of pain in OA. (22) This multifactorial nature also makes it unlikely for synovitis fully explain pain, even with perfect measurement.

We found strong associations between increases in soft tissue swelling and increases in ultrasound features, except for effusion, with comparable performance for GLOESS and synovial thickening. The strongest effect was seen for Doppler signal, where an association between decreasing Doppler signal and disappearance of soft tissue swelling was also present. This may be because joints with Doppler signal represent joints with more severe inflammation, making it more likely for soft swelling to also be present and leading to stronger associations. It is important to note that soft tissue swelling established on physical examination does not differentiate between effusion and synovial thickening. The two may thus both explain part of the swelling felt, resulting in weaker associations for the separate features.

There are some considerations regarding the GLOESS score. First, an increase in either Doppler signal or synovial thickening score causes an increase in the GLOESS score, whereas both features need to decrease in order for the GLOESS to decrease. The GLOESS can thus be expected to be especially sensitive to increases. Second, the Doppler signal score is determined by the percentage of the area of synovial tissue that shows a signal. A decrease in synovial thickening thus also affects the Doppler score. If the surface of synovial thickening and the amount of Doppler signal both decrease by half, the ratio remains the same. The synovitis score drops, but the Doppler score and thus the GLOESS score remain the same. The separate scores for Doppler signal and synovial thickening may thus remain relevant to explain what underlies the GLOESS composite. A benefit of the GLOESS is that a decrease is more likely to capture a "true" decrease, that is less likely to flare if treatment is stopped. Combining the Doppler signal and synovial hypertrophy into one composite also allows the scorer to leverage the benefits of both scores. This may result in more comparable outcomes on machines with different sensitivities for the different imaging modalities, a known problem. (26) Doppler signal rarely occurs in healthy joints and may support establishing synovitis in a joint with doubtful synovial hypertrophy, while synovial hypertrophy can compensate for lower sensitivity for Doppler signal. (11)

Our study has some limitations. The relatively short follow-up duration did not allow us to assess long term changes in both ultrasound features, clinical outcomes and their association. Our results may also not be generalizable to all different ultrasound machines. The highly selective nature of inclusion criteria used in this trial may limit generalizability to other hand OA trials and cohorts. Furthermore, given the low prevalence of Doppler signal in hand OA, we may have lacked power to detect all associations with this feature.

In this study, responsiveness and association with the clinical outcomes joint tenderness and soft issue swelling was shown for the GLOESS score in inflammatory hand OA. How-

ever, findings were comparable to ultrasound synovial thickening scores in particular and no additional value could be shown in this setting. A number of considerations regarding the GLOESS were raised, indicating a need for further exploration and investigation of this scoring system for use in patients with hand OA.

Competing interest statement

MK reports the following, all outside the current study: Grant from IMI-APPROACH. Royalties or licences from Wolters Kluwer and Springer Verlag, paid to the institution. Fees for consulting/advisory boards by Pfizer, UCB, CHDR, GSK, Novartis and Peptinov, all paid to the institution. Payment or honoraria for lectures or presentations from Novartis, paid to the institution. Roles on the OARSI board (member), EULAR council (member advocacy committee EULAR) and presidency of the Dutch Society for Rheumatology. For the current study, MK reports funding from the Dutch arthritis society, paid to the institution. The other authors report no competing interests.

Author contributions

CM and MCK contributed equally to this work. CvdM, MCK and MK designed the study. MCK, FPBK and MK collected the data. CM, MCK, and MK analysed the data. CvdM, MCK, MADA, FPBK, FRR, and MK interpreted the data and wrote the report. All authors approved the final version of the manuscript. CM and MCK are the guarantors of this manuscript.

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Data sharing statement

The data underlying this article cannot be shared publicly due to the privacy of the participants of the HOPE study and legal reasons (HOPE study participants did not sign informed consent to make their data publicly available).

Patient and public involvement

Patient partners were involved in the development and execution of the study and written information to patients.

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APPENDIX 1

Table A1. Calculation of GLOESS score

GLOESS score	Individual features	
	Grayscale synovial thickening	Doppler
0	0	0
1	1	0
	1	1
2	2	0
	2	1
	2	2
	1	2
3	3	0
	3	1
	3	2
	3	3
	2	3
	1	3

Conversion of individual features to GLOESS scores. In case of missing Doppler scores, the synovial thickening score was used to determine the GLOESS. In case of missing synovial thickening score, the GLOESS was determined to be missing for that joint.

APPENDIX 2: POPULATION CHARACTERISTICS

	Total (n=92)	Prednisolone (n=46)	Placebo (n=46)
Age, years; Mean (SD)	63.9 (8.8)	62.2 (8.8)	65.6 (8.5)
Sex, female; n (%)	73 (79)	38 (83)	35 (76)
BMI, kg/m^2; Mean (SD)	27.2 (4.6)	26.9 (4.4)	27.4 (4.9)
VAS pain fingers; Mean (SD)	54.0 (20.5)	54.4 (21.8)	53.6 (19.3)
AUSCAN pain; Mean (SD)	10.7 (3.3)	11.3 (3.3)	10.2 (3.1)
AUSCAN function; Mean (SD)	18.8 (7.4)	18.6 (7.8)	19.0 (7.1)
KL sum score; median (IQR)	38 (28.5-46.5)	33 (26-45)	41 (30-47)
Erosive disease; n (%)	67 (73)	34 (74)	33 (72)

BMI = Body Mass Index. VAS = Visual Analogue Scale. AUSCAN = Australian Canadian Hand Osteoarthritis Index. KL = Kellgren-Lawrence. Some data contained in this table was previously published in the original analysis of the HOPE trial. (4)

APPENDIX 3

Effusion	N joints	N affected	N scored 0	N scored 1	N scored 2	N scored 3
All joints	2740	787 (28.7)	1953 (71.3)	527 (19.2)	187 (6.8)	73 (2.7)
PIP	728	299 (41.1)	429 (58.9)	191 (26.2)	82 (11.3)	26 (3.6)
DIP	731	291 (39.8)	440 (60.2)	211 (28.9)	60 (8.2)	20 (2.7)
MCP	920	53 (5.8)	867 (94.2)	49 (5.3)	4 (0.4)	0 (0)
IP	183	126 (68.9)	57 (31.1)	60 (32.8)	39 (21.3)	27 (14.8)
CMC	178	18 (10.1)	160 (89.9)	16 (9.0)	2 (1.1)	0 (0)

Numbers of joints with effusion scores. Values presented as number (%), with percentage based on the row totals

Doppler signal	N joints	N affected	N scored 0	N scored 1	N scored 2	N scored 3
All joints	2741	336 (12.3)	2405 (87.7)	160 (5.8)	119 (4.3)	57 (2.1)
PIP	729	163 (22.4)	566 (77.6)	63 (8.6)	61 (8.4)	39 (5.3)
DIP	731	88 (12.0)	643 (88.0)	44 (6.0)	32 (4.4)	12 (1.6)
MCP	920	35 (3.8)	885 (96.2)	25 (2.7)	8 (0.9)	2 (0.2)
IP	183	17 (9.2)	166 (90.7)	11 (6.0)	3 (1.6)	3 (1.6)
CMC	178	33 (18.5)	145 (81.5)	17 (9.6)	15 (8.4)	1 (0.6)

Numbers of joints with Doppler signal scores. Values presented as number (%), with percentage based on the row totals

Synovial thickening	N joints	N affected	N scored 0	N scored 1	N scored 2	N scored 3
All joints	2741	1150 (42.0)	1591 (58.0)	805 (29.4)	269 (9.8)	76 (2.8)
PIP	729	521 (71.5)	208 (28.5)	299 (41.0)	168 (23.0)	54 (7.4)
DIP	731	332 (45.4)	399 (54.6)	268 (36.7)	51 (7.0)	13 (1.8)
MCP	920	126 (13.7)	794 (86.3)	102 (11.1)	19 (2.1)	5 (0.5)
IP	183	99 (54.1)	84 (45.9)	81 (44.3)	14 (7.7)	4 (2.2)
CMC	178	72 (40.4)	106 (59.6)	55 (30.9)	17 (9.6)	0 (0)

Numbers of joints with Synovial thickening scores. Values presented as number (%), with percentage based on the row totals

GLOESS	N joints	N affected	N scored 0	N scored 1	N scored 2	N scored 3
All joints	2737	1150 (42.1)	1587 (58.0)	766 (28.0)	280 (10.2)	104 (3.8)
PIP	727	521 (71.7)	206 (28.3)	288 (39.6)	163 (22.4)	70 (9.6)
DIP	730	332 (45.5)	398 (54.5)	249 (34.1)	62 (8.5)	21 (2.9)
MCP	919	126 (13.7)	793 (86.3)	102 (11.1)	18 (2.0)	6 (0.7)
IP	183	99 (54.1)	84 (45.9)	78 (42.6)	15 (8.2)	6 (3.3)
CMC	178	72 (40.4)	106 (59.6)	49 (27.5)	22 (12.4)	1 (0.6)

Numbers of joints with GLOESS scores. Values presented as number (%), with percentage based on the row totals

APPENDIX 4

Crude models of cross-sectional associations of ultrasound markers with joint tenderness and soft swelling

	Tender joints; N (%)	Odds ratio (95% CI)	Soft swollen joints; N (%)	Odds ratio (95% CI)
Effusion				
0 (n=1953)	273 (14.0)	1	176 (9.0)	1
1 (n=527)	117 (22.2)	1.80 (1.44-2.25)	99 (18.8)	2.33 (1.75-3.13)
2 (n=187)	88 (47.1)	5.15 (3.68-7.20)	58 (31.0)	4.44 (3.22-6.12)
3 (n=73)	30 (41.1)	3.53 (1.92-6.49)	27 (37.0)	6.04 (3.60-10.12)
Doppler signal				
0 (n=2405)	353 (14.7)	1	225 (9.4)	1
1 (n=160)	61 (38.1)	3.92 (2.76-5.58)	44 (27.5)	3.67 (2.27-5.94)
2 (n=119)	56 (47.1)	6.03 (4.32-8.42)	49 (41.2)	7.23 (4.48-11.67)
3 (n=57)	39 (68.4)	11.52 (6.78-19.57)	43 (75.4)	30.55 (16.84-55.42)
Synovial thickening				
0 (n=1591)	171 (10.8)	1	96 (6.0)	1
1 (n=805)	186 (23.1)	2.66 (2.10-3.77)	122 (15.2)	2.70 (1.94-3.77)
2 (n=269)	110 (40.9)	6.33 (4.71-8.50)	93 (34.6)	8.28 (5.55-12.36)
3 (n=76)	42 (55.3)	11.77 (7.04-19.68)	50 (65.8)	31.70 (18.12-55.45)
GLOESS				
0 (n=1587)	171 (10.8)	1	96 (6.1)	1
1 (n=766)	166 (21.7)	2.45 (1.92-3.12)	106 (13.8)	2.41 (1.70-3.43)
2 (n=280)	110 (39.3)	5.97 (4.49-7.93)	90 (32.1)	7.36 (4.91-11.04)
3 (n=104)	62 (59.6)	13.11 (8.42-20.41)	69 (66.4)	31.17 (19.39-50.10)

Cross sectional associations of ultrasound markers with joint tenderness. Score of 0 as index for each ultrasound marker. Analyses adjusted for age, sex, body mass index and clustering of joints within patients. CI = Confidence interval