Inflammation as a target for treatment in hand osteoarthritis

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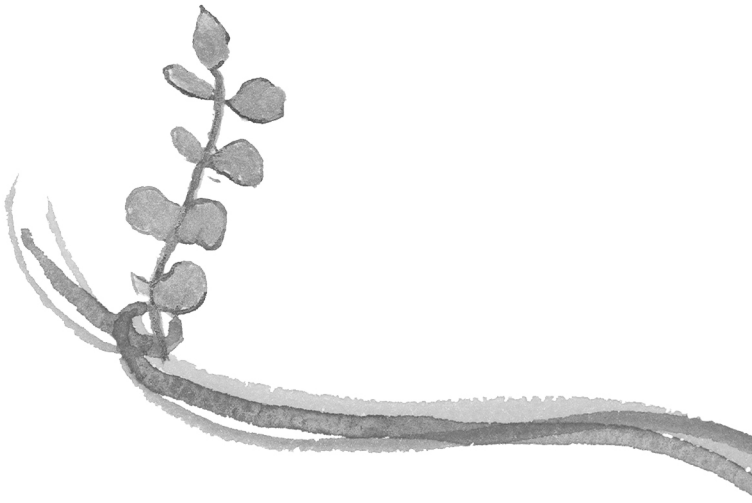
CHAPTER 7

In thumb base osteoarthritis structural damage is more strongly associated with pain than synovitis



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ABSTRACT

Objective. Osteoarthritis in thumb base joints (first carpometacarpal (CMC-1), scaphotrapeziotrapezoid (STT)) is prevalent and disabling, yet focussed studies are scarce. Our aim was to investigate associations between ultrasonographic and magnetic resonance imaging (MRI) inflammatory features, radiographic osteophytes, and thumb base pain in hand osteoarthritis patients.

Design. Cross-sectional analyses were performed in cohorts with MRI (n=202) and ultrasound measurements (n=87). Pain upon thumb base palpation was assessed. Radiographs were scored for CMC-1/STT osteophytes. Synovial thickening, effusion and power Doppler signal in CMC-1 joints were assessed with ultrasound. MRIs were scored for synovitis and bone marrow lesions (BMLs) in CMC-1 and STT joints using OMERACT-TOMS. Associations between ultrasound/MRI features, osteophytes, and thumb base pain were assessed. Interaction between MRI features and osteophytes was explored.

Results. In 289 patients (mean age 60.2, 83% women) 139/376 thumb bases were painful. Osteophyte presence was associated with pain (MRI cohort: odds ratio (OR) 5.1 (2.7-9.8)). Ultrasound features were present in 25-33% of CMC-1 joints, though no associations were seen with pain. MRI-synovitis and BMLs grade ≥2 were scored in 25% and 43% of thumb bases, and positively associated with pain (OR 3.6 (95% CI 1.7-7.6) and 3.0 (1.6-5.5)). Associations attenuated after adjustment for osteophyte presence. Combined presence of osteophytes and MRI-synovitis had an additive effect.

Conclusions. Ultrasonographic and MRI inflammatory features were often present in the thumb base. Osteophytes were more strongly associated with thumb base pain than inflammatory features, in contrast to findings in finger OA studies, supporting thumb base osteoarthritis as a distinct phenotype.

INTRODUCTION

The thumb base is a unique complex of articulations within the hand, consisting of several joints, including the first carpometacarpal (CMC-1) and scaphotrapeziotrapezoid (STT) joints. The STT joint is one of the intercarpal joints and involves multiple articulations, including those between the scaphoid and trapezium bone, and between the scaphoid and trapezoid bone. In contrast to the other finger joints, the CMC-1 joint is a saddle joint, allowing a high range of motion, yet at the cost of joint stability.[1,2] Moreover, biomechanical studies have shown that the forces on this joint are high, and that the load on the CMC-1 joint is significantly higher compared to more distally located finger joints.[3,4]

Osteoarthritis (OA) often affects the thumb base, causing pain and functional disability.[5] Previous studies have shown that involvement of the CMC-1 joint contributes considerably to the disease burden of hand OA patients.[6] Thumb base OA has been hypothesized to comprise a separate hand OA subset, since it is associated with different risk factors and outcomes than interphalangeal OA.[5] For example, studies have shown that mechanical factors seem to constitute a far more important factor in thumb base OA development, with associations of CMC-1 subluxation, higher maximal grip strength, and hypermobility to CMC-1 but not (distal) interphalangeal joint OA.[7-10] However, much is still unknown about the pathophysiology of thumb base OA, and possible distinctions with interphalangeal OA.

Structural abnormalities on radiographs, including osteophytes, subchondral bone sclerosis, and joint space narrowing (JSN), are a hallmark of the disease. An overview of studies assessing the association between structural damage and clinical signs and symptoms, concluded that a positive association between radiographic hand OA and hand pain existed, although the association was rather weak.[11] A more recent study found similar associations.[12] Yet studies assessing this relationship on joint level, taking into account patient effects, have reported strong dose-response associations.[13,14]

Magnetic resonance imaging (MRI) and ultrasound (US) studies from the recent past have further increased our insights in hand OA, by providing the opportunity to assess other structures than bone, such as the cartilage, synovium and subchondral bone. In US studies it was shown that inflammatory signs such as grey-scale synovitis and power Doppler signal (PDS) are frequently present in the finger joints of hand OA patients,[15] and that these are associated with pain. MRI studies also showed an association between synovitis and bone marrow lesions (BMLs) and pain.[16,17] Moreover, Liu *et al* found that after adjustment for synovitis and BMLs, structural damage (defined as Kellgren-Lawrence grade 2 or more) was no longer statistically significantly associated with pain, while the point estimate of both MRI features barely changed.[17] In the study by Haugen *et al* osteophytes were also no longer statistically significantly associated with pain after adjustment for other MRI features, including synovitis and BMLs.[16] Thus far, however, imaging studies have focussed on the interphalangeal joints or investigated all hand joints without differentiating between different joint groups.

Studies aimed specifically at thumb base OA, are lacking. The objective of this study therefore, was to investigate the associations between US and MRI inflammatory features, structural damage and pain in the thumb base of hand OA patients, taking advantage of the newly developed OMERACT thumb base OA MRI scoring system (TOMS).[18]

METHODS

Patients

Cross-sectional data from hand OA patients from three distinct cohorts were used in this study. Analyses exploring associations with MRI features were performed in patients from the Hand OSTeoArthritis in Secondary care (HOSTAS) study, an ongoing observational cohort including consecutive patients from the outpatient clinic of the Leiden University Medical Center (LUMC) with primary hand OA diagnosed by their treating rheumatologist. Participants who underwent MRI of the right thumb base at baseline were included in the present study (n=202, in this paper referred to as 'MRI cohort'). Analyses exploring associations with US features were performed in patients participating in the EChography in Hand OA (ECHO, n=63) and the Etanercept in Hand OA (EHOA, n=24) study at the Leiden University Medical Center (in total n=87, together referred to as 'US cohort'). Patients from the US cohort were required to fulfil the American College Rheumatology criteria for hand OA.[19] Local medical ethics committee approval was obtained for the three cohorts. All participants gave written informed consent. Details on recruitment and selection of the three cohorts have been published elsewhere.[15,20,21]

Clinical assessment

All patients underwent physical examination by trained research nurses, who assessed presence of pain upon palpation in the thumb base (absent/present). Clinical assessment was performed on the same day as the MRI or US assessment. Patients also indicated whether their thumb base was currently painful on a standardized hand diagram (self-reported thumb base pain, yes/no), the amount of current hand pain on a visual analogue scale (VAS, 0-100 mm) and completed the Australian/Canadian Osteoarthritis Hand Index (AUSCAN).[22]

Imaging

MRI

MRIs of the base of the thumb were acquired on a 1.5T extremity MRI unit (GE, Wisconsin, USA) using a 100 mm coil. A general wrist acquisition was used. MRIs were acquired according to standard protocol, including T1-weighted (T1w) fast spin echo (FSE) images in coronal and axial planes (TR/TE 575/11.2 ms, slice thickness (ST) 2.0 and 3.0 mm, slice gap (SG) 0.2 and 0.3 mm), and T2w FSE images with frequency-selective fat-saturation (fs) in coronal and axial planes (TR/TE 3000/61.8 ms and 3000/60 ms, ST 2.0 and 3.0 mm, SG 0.2 and 0.3 mm). Synovitis and BMLs were scored in the CMC-1 and STT joint (grade 0-3) by two well-trained readers (FK, SB) according to the OMERACT TOMS.[18] In absence of post-contrast images, synovitis was evaluated on T2w-fs images, as advised in the original publication.[12] BMLs were evaluated in proximal and distal joint parts separately, so the proximal part of the first metacarpal bone and distal half of the trapezium were evaluated for the CMC-1 (range 0-6), and for the STT the proximal half of the trapezium and trapezoid and the distal half of the scaphoid were scored (range 0-9). Intraclass correlation coefficients (ICCs; average measure, mixed-effect, absolute agreement) were calculated to assess inter-reader reliability, which was moderate for synovitis (CMC-1: 0.65, STT: 0.58) and excellent for BMLs (CMC-1: 0.92, STT: 0.91). A consensus score was reached when one reader had scored

synovitis grade 0-1 (absent/minimal) while the other had scored 2-3 (moderate/severe) (n=41 cases). The two readers re-assessed these cases together, and decided on a consensus score. At all times, readers were blinded for clinical characteristics and radiographic scores. The average score of the two readers, or the consensus score if applicable, was used for all analyses. An aggregated thumb base synovitis score was also calculated (synovitis grade 0-1 in both thumb base joints vs synovitis grade 2 or higher in at least one joint), and similarly for BMLs.

Ultrasound

US was performed by two ultrasonographers, who scored together in consensus during the examination, using a Toshiba Applio scanner (Toshiba medical systems, Tustin, California) with a 10-14 MHz linear array transducer. Settings were optimised by an application specialist of the manufacturer, and were identical and maintained stable throughout both studies.[15,23] The CMC-1 joint of both hands was evaluated on a semi-quantitative scale (0-3) for synovial thickening effusion and PDS as described previously.[15] Intra-observer reliability has been published before and was good to excellent in both studies (ICC 0.62-0.91).[15,23] The ultrasonographers were blinded for clinical characteristics and radiographic scores. Due to the low prevalence of joints with grade 3 synovial thickening, effusion or PDS grade, grades 2 and 3 were combined in the analyses.

Hand radiographs

Dorso-volar hand radiographs were scored for osteophytes and JSN in the CMC-1 (0-3) and STT (0-1) joints according to the Osteoarthritis Research Society International (OARSI) atlas by a single reader in each separate study.[24] Intra-reader reliability of all readers was good to excellent (ICCs 0.73-0.94).[13,25] Readers were blinded for clinical characteristics and US or MRI features.

Statistical analyses

Associations between US or radiographic features and pain on palpation of the thumb base were assessed on joint level using generalized estimating equations (GEE), accounting for the assessment of two CMC-1 joints per patient. In the MRI cohort, associations between synovitis, BMLs or osteophytes and pain were analysed using logistic regression. Interaction between MRI abnormalities and radiographic osteophytes were subsequently explored by stratifying for absence/presence osteophytes. Analyses were adjusted for relevant confounders (sex, body mass index (BMI)). Analyses were performed using SPSS version 23.0 and Stata SE version 14.1.

RESULTS

Study population

Demographic and clinical characteristics of the 289 patients included in this study are presented in table 1, split by imaging modality. Overall, patients in the US and MRI cohorts had similar characteristics, and reflect a typical hand OA population from secondary care. In the cohort with MR imaging, the prevalence of thumb base joints painful on palpation was somewhat higher (42% compared to 31%).

Imaging features in the thumb base

In table 1 the imaging characteristics of the thumb base joints are presented. Imaging features of the patients with US on patient level are presented in supplementary table 1. Around 25% of CMC-1 joints in the US cohort presented with synovial thickening and/or positive PDS, while 15% of CMC-1 joints in the MRI cohort had moderate to severe MRI-synovitis. In both cohorts, the prevalence of CMC-1 osteophytes was higher than of inflammatory features in that joint. MRI-synovitis in the STT joint had a similar prevalence as in the CMC-1 (13%), while osteophytes were less commonly seen (9%). Synovitis in both joints was uncommon (7/202 thumb bases). BMLs were more prevalent than synovitis, although higher scores were not common. In general, inflammatory features were predominantly seen in thumb bases with osteophytes (e.g., 38 of 51 thumb bases with MRI-synovitis also had a CMC-1 or STT osteophyte, and 34 of 46 thumb bases with US-synovial thickening also had an osteophyte).

Associations between imaging features and pain

No association was observed between inflammatory US features and pain upon palpation of the thumb base (table 2). Synovitis and BMLs on MRI were positively associated with pain upon palpation (odds ratios (OR) 3.6 (95% confidence interval (CI) 1.7-7.6) and 3.0 (1.6-5.5), respectively). Radiographic osteophytes, however, were more strongly associated with pain upon palpation in both cohorts, and in the participants with US there was an indication of a dose-response relation (table 2). JSN showed similar positive associations with pain upon palpation (US cohort: OR 1.9 (0.8-4.9) for grade 1, up to OR 4.2 (0.8-23.2) for grade 3; MRI cohort: OR 2.2 (1.2-4.0) for JSN present vs absent). Since osteophytes and inflammatory MRI features were often present simultaneously, and both were associated with pain upon palpation, we subsequently performed analyses in which we adjusted for the presence of osteophytes. After adjustment for osteophytes, the association between MRI-synovitis or BMLs and pain upon palpation attenuated (table 2). Additional adjustment for presence of JSN did not change the point estimates (OR for MRI-synovitis of 2.2 (0.9-5.5) and for BMLs 1.2 (0.5-2.7)). Analyses with self-reported thumb base pain in the MRI cohort, which was present in 57% of patients, revealed similar results (e.g., ORs for association between MRI-synovitis and self-reported pain of 4.7 (2.1-10.3) and 2.7 (1.1-6.4) before and after adjustment for presence of osteophytes).

Interaction between inflammatory features and osteophytes

To explore the interaction between inflammatory features and radiographic damage in relation to pain upon palpation in the thumb base, analyses stratified for absence/presence of osteophytes were performed. As shown in table 3, the association of MRI-synovitis with pain upon palpation in thumb base joints without osteophytes (OR 2.7 (0.7-10.1)) was weaker than the association of isolated osteophytes and pain upon palpation (OR 4.8 (2.2-10.6)). Combined presence of osteophytes and MRI-synovitis had an additive effect. BMLs showed a similar interaction with osteophytes, although there the additive effect was small (table 3). Analyses with self-reported thumb base pain again yielded similar results (data not shown). The fraction of pain upon palpation attributable to interaction between MRI-synovitis and osteophytes was thus (9.1-6.5)/9.1 = 29%, and, similarly, the interaction between BMLs and osteophytes accounted for 8%.

Table 1. Clinical characteristics of 289 hand osteoarthritis patients (376 thumb bases).

	Patients with US (n=87)	**Patients with MRI (n=202)**
Women, n (%)	71 (81)	169 (84)
Age, years, mean (SD)	60.3 (8.8)	60.1 (8.4)
BMI, kg/m^2, mean (SD)	27.2 (4.5)	27.6 (5.0)
Fulfilling ACR criteria, n (%)	87 (100)	181 (89.6)
AUSCAN pain, 0-20, mean (SD)	9.5 (4.6)	9.1 (4.2)
VAS hand pain, 0-100, mean (SD)	47 (21.7)	36.2 (21.0)
	Thumb bases with US (n=174)	**Thumb bases with MRI (n=202)**
Pain upon palpation, n (%)	54 (31)*	85 (42)†
US features, n (%)		
Synovial thickening	46 (26)‡	
Effusion	57 (33)‡	
Power Doppler signal	44 (25)‡	
MRI features, n (%)		
Synovitis CMC-1 joint§		
Grade 0-1		167 (83)
Grade 2-3		31 (15)
Synovitis STT joint‖		
Grade 0-1		170 (84)
Grade 2-3		27 (13)
Synovitis thumb base‖		
CMC-1 and STT grade 0-1		146 (72)
CMC-1 or STT grade 2-3		51 (25)
Bone marrow lesions CMC-1 joint‖		
Grade 0-1		128 (63)
Grade 2-3		37 (18)
Grade 4-6		32 (16)
Bone marrow lesions STT joint‖		
Grade 0-1		140 (69)
Grade 2-3		42 (21)
Grade 4-9		15 (7)
Bone marrow lesions thumb base‖		
CMC-1 and STT grade 0-1		110 (54)
CMC-1 or STT grade ≥2		87 (43)
Radiographic features, n (%)		
Osteophyte CMC-1 joint		
Absent	78 (45)	111 (55)¶
Grade 1	56 (32)	51 (25)¶
Grade 2	25 (14)	22 (11)¶
Grade 3	15 (9)	17 (8)¶
Osteophyte STT joint		18 (9)¶

ACR, American College of Rheumatology; AUSCAN, Australian/Canadian osteoarthritis hand index; BMI, body mass index; CMC-1, first carpometacarpal joint; MRI, magnetic resonance imaging; STT, scaphotrapeziotrapezoid joint; US, ultrasonography. *3 joints with missing data on pain. †1 joint with missing data on pain. ‡1 joint with missing US data. §4 MRIs not evaluable for this feature. ‖5 MRIs not evaluable for this feature. ¶1 radiograph not available.

Table 2. Associations of US, MRI and radiographic features with pain upon palpation of the thumb base of hand osteoarthritis patients.

	Pain* yes/no, n	**Associations** OR (95% CI)	**Associations, adjusted for osteophytes** OR (95% CI)
Ultrasound cohort			
US features			
Synovial thickening			
Absent	40/85	1	
Grade 1	10/22	1.1 (0.5-2.6)	
Grade 2+3	4/10	1.2 (0.3-4.6)	
Effusion			
Absent	35/79	1	
Grade 1	13/25	0.9 (0.4-2.2)	
Grade 2+3	6/13	1.0 (0.3-3.1)	
Power Doppler signal			
Absent	41/86	1	
Grade 1	8/24	0.9 (0.4-2.7)	
Grade 2+3	5/7	1.5 (0.6-3.9)	
Radiographic features			
Osteophyte CMC-1 joint			
Absent	18/58	1	
Grade 1	16/40	1.2 (0.5-2.6)	
Grade 2	11/13	1.5 (0.5-4.5)	
Grade 3	9/6	5.3 (1.1-23.2)	
MRI cohort			
MRI features			
Synovitis†			
CMC-1 and STT grade 0-1	53/93	1	1
CMC-1 or STT grade 2-3	30/21	3.6 (1.7-7.6)	2.1 (0.9-4.7)
Bone marrow lesions†			
CMC-1 and STT grade 0-1	35/75	1	1
CMC-1 or STT grade ≥2	49/38	3.0 (1.6-5.5)	1.3 (0.6-2.7)
Radiographic features			
Osteophyte CMC-1 or STT‡			
Absent	28/78	1	
Present	57/38	5.1 (2.7-9.8)	

Presented ORs were adjusted for sex and BMI. AUSCAN, Australian/Canadian osteoarthritis hand index; BMI, body mass index; CMC-1, first carpometacarpal joint; MRI, magnetic resonance imaging; STT, scaphotrapeziotrapezoid joint; US, ultrasonography**.** *3 joints with missing data on pain. †5 MRIs not evaluable for this feature. ‡1 radiograph not available.

Table 3. Number of thumb base joints painful upon palpation (yes/no) and associations (OR (95% CI)) of MRI-synovitis or BMLs with pain upon palpation, stratified for osteophytes (n=196)*.

		Osteophyte CMC-1 or STT			
		Absent		**Present**	
Synovitis	**Absent**†	23/70	1	30/22	4.8 (2.2-10.6)
	Present‡	5/8	2.7 (0.7-10.1)	25/13	9.1 (3.6-23.0)
BMLs	**Absent**†	21/64	1	14/10	5.7 (2.0-16.5)
	Present‡	7/14	1.4 (0.5-4.1)	42/24	6.6 (3.1-14.0)

Presented ORs were adjusted for sex and BMI. BMI, body mass index; BML, bone marrow lesion; CMC-1, first carpometacarpal; MRI, magnetic resonance imaging; STT, scaphotrapeziotrapezoid. *196/202 patients had evaluable MRI for synovitis/BMLs and radiographs available. †Defined as CMC-1 and STT grade 0-1. ‡Defined as CMC-1 or STT grade ≥2.

DISCUSSION

This study reports on the prevalence of inflammatory features on US and MRI in thumb base joints of a large cohort of patients with hand OA, and their association with pain in comparison with radiographic damage. The prevalence of synovial thickening, effusion and PDS on US, as well as MRI-synovitis and BMLs, was similar to what has previously been reported in studies of OA finger joints.[15-17]

Positive, dose-response associations between different inflammatory US features and pain have been reported in a study that included all hand joints in the analysis.[15] MRI studies have consistently shown positive associations of synovitis and BMLs and pain in interphalangeal joints, independent of radiographic damage, with similar effect sizes as for US.[16,17] In contrast, we show that the association of US and MRI inflammatory features with pain in the thumb base is less evident than in finger joints of hand OA patients. Moreover, we found an association between radiographic damage and pain in the thumb base as expected, yet in contrast to finger OA studies this association seemed more important in predicting pain than the inflammatory features that were assessed.

In our study, associations of MRI-detected inflammation with pain were found, but this association was no longer significant after adjustment for osteophytes. US-detected inflammation showed no association with pain. This difference in results may be due to small differences in patient characteristics of the cohorts, or due to differences between the imaging modalities. For example, US and MRI do not measure exactly the same aspect of inflammation, supported by moderate agreement between these modalities found in previous studies comparing synovitis on US and MRI.[23,26] US of the CMC-1 could also be hampered by the location of the joint (i.e., on MRI, both the radial and ulnar side of the joint can be visualized).

The observed differences between the results of our study and previous finger OA studies could indicate a difference in the underlying pathogenesis of finger and thumb base OA. In the thumb base, mechanical influences likely play a prominent role, while inflammation may be relatively more important in the pathogenesis of interphalangeal OA. The different

role of mechanical influences may be due to the different joint types and associated range of motion (saddle joint with multidirectional movements versus hinge joint with unidirectional movements), and the higher load on the thumb base than on the interphalangeal joints.[3,4] The hypothesis of thumb base OA as a distinct hand OA subset is also supported by studies showing associations with different risk factors and outcomes than interphalangeal OA.[5] Furthermore, trials investigating the effect of intra-articular injections of the CMC-1 joint with corticosteroids have shown conflicting results, and a recent meta-analysis demonstrated that intra-articular corticosteroid injections did not result in more pain relief than placebo injections.[27] In contrast, one placebo-controlled double-blind trial of intra-articular corticosteroid injections for interphalangeal OA did show positive results, although to date no trials have been performed to confirm this finding.[28]

To our knowledge, this is the first large cohort of hand OA patients with MRI of the thumb base, besides two small studies (n=9 and n=12) assessing cartilage visualization on thumb base MRIs.[29,30] It is also the first study to date investigating the role of inflammation in the thumb base joints of hand OA patients separately from the other finger joints. Some limitations have to be acknowledged. In this cohort, contrast-enhanced MR images were not available, and therefore MRI-synovitis was assessed on T2w-fs images. The disadvantage of T2w-fs images is that it is not possible to distinguish between synovitis and effusion, which may have led to an underestimation of the association between synovitis and pain. However, the inflammatory features on US even showed no associations with pain, making it less likely that we underestimated the association. Furthermore, we did not have data of patients who underwent both US and MRI examination, yet the observation that our results are similar in three different cohorts, using two different imaging modalities, also strengthens our findings. However, the US protocol did not include assessment of the STT joint, and therefore we cannot compare the findings of the US and MRI for the STT. In the analyses of the MRI cohort, the CMC-1 and STT joint were combined, since the outcome (pain on palpation of the thumb base) was assessed for the thumb base and not the separate joints, and the number of participants in each subgroup would become too small to draw robust conclusions. In this study, other, less common, radiographic features of structural damage, such as erosions, cysts and sclerosis, were not evaluated, and inclusion of these in future studies would be of interest. Finally, this is a cross-sectional study, precluding the assessment of causal relationships, or of the effect of fluctuation of the assessed inflammatory features over time.

In conclusion, in this study we have confirmed that inflammatory features on US and MRI are also present in the thumb base of hand OA patients, yet we found that radiographic osteophytes were more strongly associated with thumb base pain than these inflammatory features. Our findings are in contrast to previous studies in finger OA, supporting thumb base OA as a distinct hand OA phenotype. Future studies are warranted to further elucidate the different role of structural damage and inflammation in thumb base and interphalangeal OA, and possible consequences of these differences for treatment of hand OA patients.

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