Title: EULAR RECOMMENDATIONS FOR THE USE OF IMAGING IN THE CLINICAL MANAGEMENT OF PERIPHERAL JOINT OSTEOARTHRITIS

Authors:

Garifallia Sakellariou[1] *****, Philip G. Conaghan[2 *], Weiya Zhang[3], Johannes W J Bijlsma[4], Pernille Boyesen[5], Maria Antonietta D'Agostino[6], Michael Doherty[3], Daniela Fodor[7], Margreet Kloppenburg[6], Falk Miese[9], Esperanza Naredo[10], Mark Porcheret[11], Annamaria Iagnocco[12].

* contributed equally to this research

Corresponding author:

Professor Philip G Conaghan

Leeds Institute of Rheumatic and Musculoskeletal Medicine

Chapel Allerton Hospital

Leeds, LS7 4SA

United Kingdom

Ph: +44 113 3924883

Fax: +44 113 3924991

Email: p.conaghan@leeds.ac.uk

Affiliations:

1 Chair and Division of Rheumatology, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy

2 Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and National Institute of Health Research Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK.

3 Academic Rheumatology, Clinical Sciences Building, University of Nottingham, Nottingham City Hospital, Nottingham, UK

4 Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands

5 Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

6 APHP, Hôpital Ambroise Paré, Service de Rhumatologie, Boulogne-Billancourt; INSERM U1173, Laboratoire d'Excellence INFLAMEX, Université Paris Ouest-Versailles St.-Quentin, Saint Quentin en Yvelines, France

7 2nd Internal Medicine Department, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

8 Department of Rheumatology, Leiden University Medical Center (LUMC), Leiden, The Netherlands

9 University Dusseldorf, Medical Faculty, Department of Diagnostic and Interventional Radiology, Dusseldorf, Germany

10 Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

11 Research Institute for Primary Care and Health Sciences, Keele University, Keele, UK

12 Rheumatology Unit, Dipartimento di Scienze Cliniche e BIologiche, Università degli Studi di Torino, Turin, Italy

Keywords: osteoarthritis, ultrasonography, magnetic resonance imaging

Word count: 2988

ABSTRACT

Objective: The increased information provided by modern imaging has led to its more extensive use. Our aim was to develop evidence based recommendations for the use of imaging in the clinical management of the commonest arthropathy, osteoarthritis (OA).

Methods: A task force (including rheumatologists, radiologists, methodologists, primary care doctors and patients) from 9 countries defined 10 questions on the role of imaging in OA to support a systematic literature review (SLR). Joints of interest were the knee, hip, hand and foot; imaging modalities included conventional radiography (CR), MRI, ultrasonography, CT and nuclear medicine. PubMed and EMBASE were searched. The evidence was presented to the task force who subsequently developed the recommendations. The strength of agreement for each recommendation was assessed.

Results: 17,011 references were identified from which 390 studies were included in the SLR. Seven recommendations were produced, covering: the lack of need for diagnostic imaging in patients with typical symptoms; the role of imaging in differential diagnosis; the lack of benefit in monitoring when no therapeutic modification is related, though consideration is required when unexpected clinical deterioration occurs; CR as the first choice imaging modality; consideration of how to correctly acquire images; and the role of imaging in guiding local injections. Recommendations for future research were also developed based on gaps in evidence, such as the use of imaging in identifying therapeutic targets, and demonstrating the added value of imaging.

Conclusions: These evidence-based recommendations and related research agenda provide the basis for sensible use of imaging in routine clinical assessment of people with OA.

INTRODUCTION

Osteoarthritis (OA) is a major cause of pain and disability worldwide. Although conventional radiography (CR) is the most commonly used technique to evaluate structural features of OA, significant advances have been made in the field of imaging over the last decade, allowing a more accurate evaluation of both bone and soft-tissue abnormalities. While newer modalities such as magnetic resonance imaging (MRI) and ultrasound have increased the understanding of the multiple pathologies contributing to the OA phenotype, it is not clear how they should be used in routine care. The role of imaging in clinical practice for OA diagnosis, management and follow-up has not been clearly defined. Despite this limitation, the increased availability of modern imaging has expanded its use, with possible excesses [1] leading to increased costs. A European League Against Rheumatism (EULAR) task force was therefore created to develop evidence-based recommendations on the use of imaging in the management of symptomatic, peripheral joint OA, for clinicians who treat OA in their clinical practice.

METHODS

A group selected from a range of expertise (rheumatologists, radiologists, primary care physicians, methodologists and patients) and representing 9 countries were included in the task force. During the first meeting, the focus of the recommendations (symptomatic OA affecting the knee, hip, hand or foot) was clarified. Clinically relevant questions on the application of imaging in OA were proposed and 9 research questions were selected by consensus to guide a detailed systematic literature review (SLR). Two questions that covered the same area were subsequently combined. The areas of diagnosis, prognosis, follow-up and treatment were covered. The questions were rephrased according to the PICO (population, intervention, comparison, outcome) (see supplementary fileS1 Research Questions).
A SLR was performed by one of the authors (GS), with checking of all extractions by one of 3 other authors experienced in SLRs. The search strategies were based on both MeSh (Medical Subject Headings) terms and free text. The searches were performed separately for each joint (see supplementary file S2 Search Strategies). The titles and abstracts of the references that were retrieved were screened by the same author according to pre-defined inclusion and exclusion criteria, based on the PICO for each question, and potentially relevant articles were evaluated in their full text. Studies in English including adults (≥18) with symptomatic OA of the knee, hip, hand and foot were eligible for inclusion. Imaging modalities included were CR, MRI, ultrasonography (US), computed tomography (CT) and nuclear medicine techniques (scintigraphy, positron emission tomography, PET). Randomized controlled trials,

systematic reviews and meta-analyses, controlled clinical trials, case-control studies, cross-sectional studies and cohort studies were eligible for inclusion. Studies had to examine the role of imaging in the following: in making a diagnosis of OA; in detecting OA elementary lesions; for differential diagnosis; in the management of OA; in predicting outcome and therapeutic response; for follow-up of disease course; to guide treatment. The same articles could be included in more than one search. Due to the variety of joint sites and imaging and the expectation of a strong degree of heterogeneity across studies, meta-analyses were not pre-specified before study selection and extraction. The methodological quality of the included studies was not assessed by quality scores, but some aspects were considered for all studies, together with design-specific indicators . For all studies, study design, sample size, setting sampling were considered. For RCTs allocation concealment, drop-out rate as well as the presence of funding, for diagnostic studies the adequacy of the reference standard, for cohort studies the presence of adjustment for confounders were also evaluated. Each aspect was evaluated separately as leading to high, low or unclear risk of bias.

During the second meeting the results of the literature review were presented and the experts developed 'over-arching' statements (background statements to preface the recommendations) and drafted 7 recommendations through a process of discussion and consensus. The number of recommendations emerged through the discussion after the presentation of the literature. To explore the presence of additional evidence concerning two recommendations, two more research questions on 1) the different performance of various radiographic views in detecting OA features and 2) the accuracy of imaging guided compared to blind joint injections were added to the original 8, with two additional literature searches (See supplementary file S1, research questions and S2, search strategies). After evaluation of these results, the Task Force confirmed the final wording of the recommendations and scored the perceived level of agreement (LOA) for each statement using a 0-10 numeric rating scale (0=fully disagree; 10=fully agree), reflecting both literature evidence and expert opinion. Recommendations for further research were then developed based on gaps in the SLRs.

RESULTS

The searches in the electronic databases (PubMed, Embase) were performed up to the end of January 2015 for the main searches and December 2015 for the additional searches. The initial search resulted in 6858 records, (615 duplicates). Of the remaining 6243 articles, 4926 were excluded based on the title and abstracts, leaving 1317 articles for detailed review. All full text articles were retrieved, 986 articles were excluded after reviewing the full text leaving 331 articles for inclusion (supplementary file S3, online only). The hand search of the references of the included

studies identified 33 additional articles, leading to a total of 364 studies finally analyzed. Articles that were relevant to more than one research question were used for each question as appropriate. The number of articles included for each site and imaging are shown in figure S4, available online only. The complete results of the SLR with references are reported in the supplementary file S5.

The additional search on the comparison of different radiographic views resulted in 4774 articles (225 duplicates). Of the remaining 4549, 4496 were excluded based on the title and abstracts, leaving 53 articles for detailed review. Twenty-three articles were excluded after reviewing the full text, leaving 30 articles for inclusion. The hand search identified 1 additional article for inclusion, leading to a total of 31 articles finally included (supplementary file S6, online only).

The additional search on the added value of imaging to guide intra-articular procedures resulted in 5379 articles, (834 duplicates). Of the remaining 4545, 4520 were excluded based on the title and abstracts, leaving 25 articles for detailed review. Nineteen articles were excluded after reviewing the full text leaving 6 articles for inclusion. The hand search identified 2 additional articles for inclusion, leading to a total of 8 articles finally included (supplementary file S7, online only). The complete results of the additional searches with references are reported in the supplementary file S8.

Recommendations

Table 1 summarizes the 7 recommendations with their corresponding level of evidence and LOA. Each recommendation is presented in detail below.

Table 1. Recommendations, levels of evidence and level of agreement (LOA)

Recommendation	Level of evidence	LOA, mean (95% CI)
1. Imaging is not required to make the diagnosis in patients with typical* presentation of OA. *typical features include: usage-related pain, short duration morning stiffness, age>40, symptoms affecting one or a few joints.	III-IV	8.7 (7.9, 9.4)
2. In atypical presentations imaging is recommended to help confirm the diagnosis of OA and/or make alternative or additional diagnoses.	IV	9.6 (9.1, 10)
3. Routine imaging in OA follow-up is not recommended. However, imaging is recommended if there is unexpected rapid progression of symptoms or change in clinical characteristics to determine if this relates to OA severity or an additional diagnosis.	III-IV	8.8 (7.9, 9.7)
4. If imaging is needed, conventional (plain) radiography should be used before other modalities. To make additional diagnoses, soft tissues are best imaged by US or MRI and bone by CT or MRI.	III-IV	8.7 (7.9, 9.6)
5. Consideration of radiographic views is important for optimizing detection of OA features; in particular for the knee, weight-bearing and patellofemoral views are recommended.	III	9.4 (8.7, 9.9)
6. According to current evidence, imaging features do not predict non-surgical treatment response and imaging cannot be recommended for this purpose.	II-III	8.7 (7.5, 9.7)
7. The accuracy of intra-articular injection depends on the joint and on the skills of the practitioner and imaging may improve accuracy. Imaging is particularly recommended for joints that are difficult to access due to factors including site (e.g. hip), degree of deformity and obesity.	III-IV	9.4 (8.9, 9.9)

Categories of evidence: **Ia**, evidence for meta-analysis of randomized controlled trials; **Ib**, evidence from at least one randomized controlled trial; **IIa**, evidence from at least one controlled study without randomization; **IIb**, evidence from at least one other type of quasi-experimental study; **III**, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies; **IV**, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
LOA: 0-10 numerical rating scale

Overarching statements

1. These recommendations pertain only to symptomatic OA.
2. Imaging abnormalities of OA are commonly seen especially with increasing age.
3. Joint symptoms are also common and increase with age. Symptoms are not always causally related to imaging abnormalities.
4. Full history and examination is always required before considering the need for investigations, including imaging.
5. Modern imaging modalities provide the capability to detect a wide range of soft tissue, bony and cartilage pathology in OA. However, the increased information provided has not yet had any influence on clinical decision making with respect to management,

Making a diagnosis of OA

Recommendation 1: Imaging is not required to make the diagnosis in patients with typical* presentation of OA. *typical features include: usage-related pain, short duration morning stiffness, age>40, symptoms affecting one or a few joints. Level of evidence: III-IV. Level of agreement (95%CI): 8.7 (7.9, 9.4)

Although many studies applied imaging for diagnostic purposes, there was a lack of studies in which imaging was applied in addition to clinical findings to evaluate its additional impact on the certainty of diagnosis, which was a predefined criterion for inclusion.

A single study examined the added value of US of hand and feet over clinical findings in a cohort of patients with suspected or confirmed arthritis. When US was added to clinical findings, the diagnostic confidence in differentiating OA from inflammatory arthritis significantly increased. [2] Due to the absence of strong evidence supporting the use of different imaging modalities at different anatomical sites, the systematic use of imaging in the diagnostic process was not recommended in cases with typical clinical presentation. However, based on the joint site and clinical presentation, imaging might be considered when diagnoses other than OA are suspected. This aspect has been taken into account in recommendation 2.

Recommendation 2: In atypical presentations imaging is recommended to help confirm the diagnosis of OA and/or

make alternative or additional diagnoses. Level of evidence: IV. Level of agreement (95%CI): 9.6 (9.1, 10)

Studies were eligible for inclusion if they investigated the added value of imaging for differential diagnosis over clinical evaluation. Among studies evaluating the application of imaging for differential diagnosis, no study evaluated the impact of the addition of imaging above clinical findings. The possible application if imaging in atypical clinical scenarios was however recognized by the experts, which included this point in the recommendation.

Monitoring disease

Recommendation 3: Routine imaging in OA follow-up is not recommended. However, imaging is recommended if there is unexpected rapid progression of symptoms or change in clinical characteristics to determine if this relates to OA severity or an additional diagnosis. Level of evidence: III-IV. Level of agreement (mean, 95%CI): 8.8 (7.9, 9.7)

A specific question addressed the use of imaging for the follow-up. The 117 studies (mostly cohort studies) retrieved covered all joint sites except the foot and all imaging modalities except CT (Figure S9). Most of the 83 included studies focused on sensitivity to change. [3-86] The remaining studies investigated the trajectories of changes of elementary lesions detected by imaging when following OA natural history or described the parallel changes between different abnormalities detected by different imaging modalities. [87-105] Only a minority of studies examined the correlation between the change in imaging features and symptoms or relevant clinical outcomes (Table 2) and only 4 US studies evaluated the change of imaging after treatment (Supplementary file S10). [106-115]

Table 2. Studies correlating changes in imaging findings with symptoms, function or clinical outcome

Study	N	Site	Study design	Imaging	Outcome	
Fukui 2010	68	Knee	Cohort	CR	Correlation between radiographic progression and pain and function scores	Progressors had more pain and disability compared to non progressors
Eckstein 2014	189	Knee	Case-control	MRI	Cartilage loss in patients undergoing TKA vs controls	OR (95%CI) for cartilage loss in patients undergoing TKA vs controls: 1.36 (1.08,1.70)
Kornaat 2007	182	Knee	Cohort	MRI	Change in BMLs/change in WOMAC pain and function	No significant differences in WOMAC pain and function depending on the changes of BMLs
Phan 2006	34	Knee	Cohort	MRI	Cartilage and BMLs/WOMAC	No significant correlation between cartilage loss, BMLs and WOMAC changes
Zhang Y 2011	651	Knee	Cohort	MRI	Change in pain status according to change in BMLs and effusion/synovitis score	Changes in BMLs and synovitis severity (worsening or improving) significantly related to the risk of frequent knee pain (p 0.006 for worsening BMLs and p 0.045 for improving BMLs. No significant correlation with changes in effusion severity.
Haugen 2013	190	Hand	Cohort	CR	Radiographic progression/incident tenderness	joints with progression had higher Odds for tenderness, joints with incident KL 3 or 4 had higher Odds for tenderness

N: number of participants; CR: conventional radiography; MRI: magnetic resonance imaging; TKA: total knee arthroplasty; OR: Odds Ratio; 95% CI: 95% confidence interval; WOMAC Western Ontario MacMaster Universities Arthritis Index; BMLs: bone marrow lesions

Moreover, there were no studies comparing clinical follow-up with imaging follow-up, or strategies adding imaging to clinical management.

The impact of imaging in the management of OA was also specifically addressed by the literature search. Three studies addressed this point. One RCT evaluating the impact of MRI in patients with knee pain assessed in a general practice setting showed that MRI led to an increase in therapeutic confidence but no significant changes in management. [116] A cross-sectional study in an orthopedic setting investigating the impact of CR over management decisions in knee OA showed that CR led to the change in the opinion in 166/400 cases. [117] A similar study evaluating the impact of CR in the assignment of priority for surgery in hip OA, showed a relative risk (95% CI) of 1.98 (1.23, 3.19) for an earlier assignment in patients with more severe radiographic scores. [118] No studies evaluated the impact of imaging for the management of hand or foot OA and no studies specifically addressed the issue of non-surgical management.

Recommendation 4: If imaging is needed, conventional (plain) radiography should be used before other modalities. To make additional diagnoses, soft tissues are best imaged by US or MRI and bone by CT or MRI. Level of evidence: III-IV. Level of agreement (95%CI): 8.7 (7.9, 9.6)

The performance of imaging in the detection of OA elementary lesions was addressed by the SLR, and highlighted heterogeneity in the use of imaging modality, lesions considered and reference standard. In fact, physical examination was frequently taken into account as reference standard, while surgery was considered in a minority of studies. Supplementary file S11 summarizes the studies with surgery as the reference standard. [119-140] As expected, the use of CR was mainly to detect bone and indirectly cartilage loss, MRI was used for bone, cartilage and soft tissues, with a single study assessing US for the evaluation of cartilage.

In general, CR was the imaging modality that was most frequently used for diagnostic, prognostic and follow-up purposes. However, no studies of the cost-effectiveness of each imaging modality or theirsequence were found. In the absence of appropriate literature, the experts decided to emphasize the role of the most easily available and less costly imaging modality, proposing as second level investigations techniques that, due to their characteristics, are more suitable for the detailed assessment of soft tissues (MRI and US) or bone (CT).

Recommendation 5: Consideration of radiographic views is important for optimizing detection of OA features; in particular for the knee, weight-bearing and patellofemoral views are recommended. Level of evidence: III. Level of agreement (95%CI): 9.4 (8.7, 9.9)

This topic was addressed by an additional research question, evaluating the optimal combination of radiographic views in OA. Twenty-seven studies comparing different views for knee OA were included. In this context, all studies involving the tibiofemoral compartment considered weight-bearing views, both in extension and various degrees of flexion. [17, 127,147-159] Studies comparing fully extended and flexed views in general showed a moderate to good agreement between the two projections and similar sensitivity and specificity in detecting cartilage damage, considering arthroscopic findings as reference. [121, 145, 146, 151, 152] The flexed views demonstrated superiority in detecting joint space narrowing, a greater sensitivity to change and reproducibility compared to extended views. [17, 153,154,156, 158, 159]

Concerning the assessment of the patellofemoral compartment, skyline views had a greater inter- and intra-reader reliability and sensitivity to change compared to lateral projections. [24, 146, 158, 159] With surgery as reference standard, the skyline view had greater sensitivity and specificity to detect cartilage damage at the patellofemoral joint. [160]

There were 5 studies assessing the hip. Three studies compared weight-bearing and supine AP views of the pelvis, one of them showing greater average and maximal joint space width detected by the weight-bearing view, the remaining showing inconsistent results. [161-165] Two studies comparing pelvis, hip and oblique views projections in terms of reliability and sensitivity to change demonstrated similar reliability for views dedicated to the hip and views including all the pelvis, with comparable sensitivity to change. [166,167] No studies assessing the hand and the foot were found.

Role in prognosis

Recommendation 6: According to current evidence, imaging features do not predict non-surgical treatment response and imaging cannot be recommended for this purpose. Level of evidence: II-III. Level of agreement (95%CI): 8.7 (7.5, 9.7)

Two specific research questions addressed the role of imaging in prognosis, referring to both the prediction of the natural history and to the prediction of non-surgical treatment outcomes. A number of studies addressed the issue of the prognostic value of imaging as predictor of the natural history of OA (Figure S12), while only a minority of studies, evaluating all joint sites, investigated the role in predicting treatment response. Due to the heterogeneity in populations, interventions, treatment and study design, a meta-analysis was not possible. In addition, progression of some imaging pathologies may have limited clinical significance. Tables 3 and 4 summarize the results of the 28

primary studies in which imaging was applied to predict treatment response. [170-193] Moreover, an existing SLR was available, without a quantitative synthesis. [194] The results on the prediction of response were mostly inconsistent across studies; for this reason the use of imaging for this purpose was not recommended.

Table 3. Summary of studies evaluating imaging in the prediction of response to treatment: systemic treatment

Study	N	Site	Study design	Imaging	Outcome	
Gudbergsen 2012	192	Knee	RCT	CR MRI	mJSW, alignment and MRI scores/pain reduction in response to very low energy diet or low energy diet	Among all radiographic and MRI parameters, only effusion score was significantly related to a reduction in pain
Gudbergsen 2011	30	Knee	RCT	CR MRI	KLG and MRI score/change in WOMAC pain and function during weight reduction at 32 weeks	No significant association between KLG and MRI score and WOMAC
Hellio le Graverand 2013	1452	Knee	RCT	CR	KLG/structural progression in patients treated with cidunistat or placebo at 96 weeks	No significant difference between KLG2 and KLG3 in terms of progression of joint space narrowing in both cidunistat and placebo group
Case 2003	82	Knee	RCT	CR	KLG and medial JSN/WOMAC response to diclofenac vs paracetamol at 12 weeks	Patients with KLG 1-2 and not 3-4 and JSN grade 0-1 compared to 2 had a better response to diclofenac vs both placebo and paracetamol
Sawitzke 2008	375	Knee	RCT	CR	KLG/radiographic progression during treatment with glucosamine, chondroitin sulphate and celecoxib at 24 months	OR for radiographic progression compared with the placebo group was <1 in patients with KLG 2 knees in all treatment groups, whereas it was>1 in patients with KLG 3 knees in all treatment groups
Mazzuca 2010	379	Knee	RCT	CR	Alignment/radiographic progression in doxycycline vs placebo at 30 months	Varus knees exhibited a greater loss of JSW than non-varus knees in patients receiving doxycycline
Knoop 2014	91	Knee	Cohort	MRI	MRI/change in WOMAC function in response to exercise program at 12 weeks	The severity of the patellofemoral damage was significantly related to less improvement
Wenham 2012	65	Hand	RCT	MRI	MRI/response to prednisolone 5 mg at 12 weeks	The baseline number of joints with definite synovitis or effusion did not correlate with OARSI response
Lequesne 2002	163	Hip	RCT	CR	JSW/structural progression in patients treated with avocado soybean at 2 years	In patients with smaller JSW treated with avocado soybean, the reduction of JSW was half than in the placebo group; no differences in patients with more JSW
Rozendaal 2009	222	Hip	RCT	CR	KLG/WOMAC pain and function, JSN in patients taking glucosamine at 2 years	Significant better WOMAC function response in patients with KLG 1 compared to KLG 2; no differences in WOMAC pain and JSN
Hoeksma 2005	103	Hip	RCT	CR	KLG/Harris Hip score and range of motion in response to manual therapy vs exercise	Better response in terms of range of motion in lower compared to higher radiographic grades

N: number of participants; RCT: randomized controlled trial; MRI: magnetic resonance imaging; CR: conventional radiography; BML: bone marrow lesions; mJSW: minimal joint space width; JSN: joint space narrowing; JSW: joint space width; WOMAC: Western Ontario Mc Master Universities Osteoarthritis index; KLG: Kellgren and Lawrence grade; OARSI: osteoarthritis research society international

Table 4. Summary of studies evaluating imaging in the prediction of response to treatment: intra-articular treatment

Study	N	Site	Study design	Imaging	Outcome	
Barrett 1990	248	Knee	cohort	CR	Radiographic severity/response to intraarticular HA at 6 months	Patients with less severe radiographic grade had a better response in terms of pain at rest, at walking and at night
Gaffney 1995	84	Knee	RCT	CR	OA severity 0-3/response to intraarticular trimacinolone vs placebo at 3 weeks	No association between improvement in VAS pain and radiographic score
Toh 2002	60	Knee	cohort	CR	Alignment, sclerosis, cysts, osteophytes, JSN/WOMAC response to intraarticular HA at 12 weeks	Patients with lateral and medial JSN had less WOMAC response compared to patients without
Pendleton 2008	86	Knee	cohort	US	US/WOMAC response to intraarticular methylprednisolone	Higher baseline US scores: significant improvements in all WOMAC subscales at 1 and 6 weeks
Chao 2010	67	Knee	RCT	US	US inflammation/WOMAC response to triamcinolone at 12 weeks	statistically significant improvement in pain subscales among without inflammatory abnormalities at US patients compared to the remaining patients
Anandacoomarasamy 2008	32	Knee	Cohort	MRI	Cartilage volume/response to intraarticular HA at 6 months	no correlation between baseline MRI measures and clinical response
Drakonaki 2011	51	Foot	Cohort	CR US	Positive therapeutic response (i.a. methylprednisolone) at 12 months	No differences in terms of response in patients showing degenerative changes only on US and those showing changes in both US and CR
Han 2014	40	Foot	Cohort	CR	Response to intraarticular HA (VAS pain) at 12 months	Patients with early radiographic stage had a better response compared to those with advanced radiographic stage at 3 and 6 months, but not at 12 months
Sun 2011	46	Foot	Cohort	CR	KLG 2 and 3/AOS, AOFAS scores in response to intraarticular HA	no significant difference in the AOS, AOFAS, or clinical balance test scores between KLG 2 and 3 at any time point
Mallinson 2013	31	Hand	Cohort	CR US	CR and US/ response to intraarticular triamcinolone at 6 weeks	No significant association between treatment response and grade for osteophytes, joint-space narrowing and capsule thickness
Atchia 2011	77	Hip	RCT	US	Synovitis/response to i.a. methylprednisolone at 6 weeks	The presence of synovitis significantly predicted the response
Rennesson- Rey 2008	55	Hip	Cohort	CR US	Effusion and KLG/OARSI response to HA at 6 months	Patients with KLG 1-2 had a better 1 months response compared to grades 3-4; non differences at 3 and 6 months, no differences in patients with or without effusion
Deshmukh 2011	220	Hip	Cohort	CR	KLG/pain relief after methylprednisolone injections at 2 weeks	Patients with KLG 3-4 had more frequently delayed relief compared to KLG 2
Robinson 2007	120	Hip	Cohort	CR US	US osteophytes and capsular thickening, KLG/WOMAC response to i.a. CS at 12 weeks	no baseline US or radiographic variable predictive of the outcome

N: number of participants; RCT: randomized controlled trial; MRI: magnetic resonance imaging; CR: conventional radiography; US: ultrasonography; VAS: visual analogue scale; HA: hyaluronic acid; JSN: joint space narrowing; WOMAC: Western Ontario Mc Master Universities Osteoarthritis index; KLG: Kellgren and Lawrence grade; OA: osteoarthritis; AOFAS Australian Orthopedic Foot and ankle society; OARSI: osteoarthritis research society international; CS: corticosteroids; i.a.: intra-articular

Treatment (imaging-guided procedures)

Recommendation 7: The accuracy of intra-articular injection depends on the joint and on the skills of the practitioner and imaging may improve accuracy. Imaging is particularly recommended for joints that are difficult to access due to factors including site (e.g. hip), degree of deformity and obesity. Level of evidence: III-IV. Level of agreement (95%CI): 9.4 (8.9, 9.9)

A search addressing the impact of imaging to guide intra-articular injections was run specifically for OA in the beginning. Including only studies comparing imaging-guided to blind procedures, 4 primary studies were found for the knee and one for the hand, and a qualitative systematic literature review for the knee (Table 5). The added value of US was addressed by 4 studies, while fluoroscopic guidance was tested in a single study. [195-199]

Table 5. Studies comparing imaging-guided to blind injections in OA

Study	N	Site	Study design	Imaging	Outcome	
Bum Park 2012	99	Knee	RCT	US	Accuracy of HA injection vs blind injection	OR (95%CI) for an accurate injection with US compared to blind: 4.68 (0.94,23.30)
Im 2006	99	Knee	RCT	US	Accuracy of HA injection vs blind injection	Accurate injections: 95.5% (US-guided) vs 77.2% (blind); p=0.01
Jang 2013	126	Knee	RCT	US	Accuracy of US guided in plain injection, US guided out of plane injections and blind injection of triamcinolone exhacetonide	Accuracy: US guided in plain 95.1%; US guided out of plain 97.7%; Blind 78% P<0.05 blind vs US guided injections
Sibbitt 2011	92	Knee	RCT	US	US guided vs blind triamcinolone in terms of pain relief, pain related to the injection, reinjection rate and cost	Significant decrease in pain only in patients treated with US guided injection; US guided procedure was related to lower pain and reinjection rate, but higher costs
Karalezli 2007	16	Hand	Cohort	CR	Fluoroscopy-guided vs blind injections of HA in the trapezio-metacarpal joint in terms of pain related to the injection	VAS pain related to the procedure: Fluoroscopic guide: 4.1 (range 3–6), anatomic guide 5.6 (range 3–7); p<0.005 No significant difference in terms of safety

N: number of participants; RCT: randomized controlled trial; US: ultrasonography; CR: conventional radiography; HA: hyaluronic acid; OR: Odds Ratio; VAS: visual analogue scale.

In order to retrieve further information on this topic, an additional search was performed (supplementary file S1 for search strategies), including studies comparing blind to guided injections in OA and also in other conditions. This search found 8 studies, of which 3 were already included in the previous results (Supplementary file S13). [200-204] Most of the studies were focused on the knee, with some studies on the hand and the foot, while no studies were found for the hip. All the additional studies investigated the impact of US. Accuracy was found to be better in imaging guided compared to blind procedures, however the results on the clinical outcomes of the injection were less consistent across studies. For this reasons the systematic use of imaging to drive injections was not recommended, leaving this tool to drive injection in specific situations, identified by the experts. Although the imaging modality is not specified in the recommendation, there is published evidence for the use of US, and imaging allows for real time evaluation of injection placement.

Future research agenda

The most important topics to drive future research were selected by the Task Force based on the (often considerable) gaps in the evidence and the needs arising from clinical practice (Table 6).

Table 6: Future Research Agenda

1	There is a need for methodologically robust studies to explore the added value of imaging (any modality) to clinical diagnosis or differential diagnosis.
2	What is the cost-effectiveness of imaging in OA clinical practice?
3	Is imaging able to help in identification of subgroups/phenotypes that may have different trajectories and enable targeted treatment based on these subgroups?
4	There is a need to understand if using imaging to measure response to therapy is of clinical benefit. This may require evaluation of novel imaging technologies that are able to sensitively detect change in relevant joint structures.
5	Quality studies are required to explore imaging (any modality) features that predict response to specific therapies.
6	There is a need for more research concerning the benefits of imaging in less commonly studied OA sites such as the foot and shoulder.
7	Specifically for hip OA, what is the added value of weight-bearing vs non weight-bearing X-rays?
8	What are the benefits of imaging-guidance in improving the efficacy of treatments?

DISCUSSION

Although a number of recommendations have been made on how to use imaging in OA clinical trials, these are the first recommendations on the use of imaging in OA in clinical practice. The development of the recommendations started from questions of clinical relevance selected by a task force of experts, with the aim to focus on topics of interest for clinical practice rather than research. The literature review identified a large number of studies, covering most joint sites. However a possible limitation of this work is that we used a search term of "osteoarthritis" and not "pain", and it is possible we missed studies that imaged painful sites without specifically mentioning OA; this may explain the paucity of foot pain studies included. Although conventional radiography was still the most frequently applied technique, a substantial number of studies focused on modern imaging, MRI and US in particular.

However, despite the amount of data available in the literature, only a small part of this information was relevant for clinical practice. For this reason, many areas needing further investigation were identified. In particular, there was a lack of strategic studies investigating the additional value of imaging over clinical findings in making a diagnosis of OA, in the management and the follow-up of the disease, and inconsistent results dealing with the prediction of the outcome of non-pharmacological treatments. The absence of good study information in these areas did not enable the Task Force to recommend systematic imaging in all these areas. A research agenda was therefore generated in order to address these topics in the future research.

In conclusion, 7 recommendations covering different areas in the routine management of OA were developed. These

are based on both available scientific evidence and expert opinion to provide a valuable and sensible guide for the use of imaging in clinical practice.

COMPETING INTERESTS

There are no competing interests.

CONTRIBUTORSHIP

GS performed the literature review, GS and PGC produced drafts of the manuscript with advice from AI and WZ. All authors were involved in the production of the recommendations and have reviewed the final manuscript.

AKNOWLEDGEMENTS

The authors would like to thank Mrs. Jaqueline Mäder for participating to the development of the recommendations.

The authors would like to thank EULAR for financial support for this work.

PGC is supported in part by the National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health FUNDING INFO This work had no funding.

ETHICAL APPROVAL INFORMATION

The approval of the Ethics committee was not required since the study did not directly involve human subjects.

DATA SHARING STATEMENT

There are no additional unpublished data available.

References

1. Petron DJ, Greis PE, Aoki SK, et al. Use of knee magnetic resonance imaging by primary care physicians in patients aged 40 years and older. Sports health 2010;2:385-90.
2. Matsos M, Harish S, Zia P, et al. Ultrasound of the hands and feet for rheumatological disorders: Influence on clinical diagnostic confidence and patient management. *Skeletal Radiol*2009;38:1049-54.
3. Wirth W, Nevitt M, Hellio Le Graverand MP, et al. Lateral and medial joint space narrowing predict subsequent cartilage loss in the narrowed, but not in the non-narrowed femorotibial compartment--data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2014;22:63-70.
4. Pessis E, Drape JL, Ravaud P, et al. Assessment of progression in knee osteoarthritis: results of a 1 year study comparing arthroscopy and MRI. *Osteoarthritis Cartilage* 2003;11:361-9.
5. Conrozier T, Mathieu P, Piperno M, et al. Selection of knee radiographs for trials of structure-modifying drugs in patients with knee osteoarthritis: A prospective, longitudinal study of Lyon schuss knee radiographs with the definition of adequate alignment of the medial tibial plateau. *Arthritis Rheum* 2005;52:1411-7.
6. Hellio Le Graverand MP, Vignon EP, Brandt KD, et al. Head-to-head comparison of the Lyon Schuss and fixed flexion radiographic techniques. Long-term reproducibility in normal knees and sensitivity to change in osteoarthritic knees. *Ann Rheum Dis* 2008;67:1562-6.
7. Mazzuca SA, Hellio Le Graverand MP, Vignon E, et al. Performance of a non-fluoroscopically assisted substitute for the Lyon schuss knee radiograph: quality and reproducibility of positioning and sensitivity to joint space narrowing in osteoarthritic knees. *Osteoarthritis Cartilage* 2008;16:1555-9.
8. Piperno M, Graverand MPHL, Conrozier T, et al. Quantitative evaluation of joint space width in femorotibial osteoarthritis: Comparison of three radiographic views. *Osteoarthritis Cartilage* 1998;6:252-9.
9. Spector TD CP, Buckland-Wright JC, Garnero P, et al. Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial. *Arthritis Res Ther* 2005;7:R625-33.
10. Mazzuca SA, Brandt KD, Buckwalter KA. Detection of radiographic joint space narrowing in subjects with knee osteoarthritis: Longitudinal comparison of the metatarsophalangeal and semiflexed anteroposterior views. *Arthritis Rheum* 2003;48:385-90.
11. Botha-Scheepers S, Kloppenburg M, Kroon HM, et al. Fixed-flexion knee radiography: the sensitivity to detect knee joint space narrowing in osteoarthritis. *Osteoarthritis Cartilage* 2007;15:350-3.
12. Cicuttini FM, Wluka AE, Hankin J, et al. Comparison of patella cartilage volume and radiography in the assessment of longitudinal joint change at the patellofemoral joint. *J Rheumatol* 2004;31:1369-72.
13. Hellio Le Graverand MP, Buck RJ, Wyman BT, et al. Change in regional cartilage morphology and joint space width in osteoarthritis participants versus healthy controls: a multicentre study using 3.0 Tesla MRI and Lyon-Schuss radiography. *Ann Rheum Dis* 2010;69:155-62.
14. Hellio le Graverand MP, Clemmer RS, Redifer P, et al. A 2-year randomised, double-blind, placebo-controlled, multicentre study of oral selective iNOS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. *Ann Rheum Dis* 2013;72:187-95.
15. Mazzuca SA, Brandt KD, Dieppe PA, et al. Effect of alignment of the medial tibial plateau and x-ray beam on apparent progression of osteoarthritis in the standing anteroposterior knee radiograph. *Arthritis Rheum* 2001;44:1786-94.
16. Pavelka KFS, Olejarova M, Gatterova J, et al. Hyaluronic acid levels may have prdictive value for the progression of knee osteoarthritis. *Osteoarthritis Cartilage* 2004;12:277-83.
17. Vignon E, Piperno M, Le Graverand MPH, et al. Measurement of radiographic joint space width in the tibiofemoral compartment of the osteoarthritic knee: Comparison of standing anteroposterior and Lyon schuss views. *Arthritis Rheum* 2003;48:378-84.
18. Wirth W, Duryea J, Hellio Le Graverand MP, et al. Direct comparison of fixed flexion, radiography and MRI in knee osteoarthritis: responsiveness data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2013;21:117-25.
19. Boegard TL, Rudling O, Petersson IF, et al. Distribution of MR-detected cartilage defects of the patellofemoral joint in chronic knee pain. *Osteoarthritis Cartilage* 2003;11:494-8.
20. Mazzuca SA, Brandt KD, Buckwalter KA, et al. Pitfalls in the accurate measurement of joint space narrowing in semiflexed, anteroposterior radiographic imaging of the knee. *Arthritis Rheum* 2004;50:2508-15.
21. Miyazaki T WM, Kawahara H, Sato M, et al. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. *Ann Rheum Dis* 2002;61:617-22.
22. Bruyere O, Henrotin YE, Honore A, et al. Impact of the joint space width measurement method on the design of knee osteoarthritis studies. *Aging Clin Exp Res.* 2003;15:136-41.
23. Gossec L, Jordan JM, Mazzuca SA, et al. Comparative evaluation of three semi-quantitative radiographic grading techniques for knee osteoarthritis in terms of validity and reproducibility in 1759 X-rays: report of the

OARSI-OMERACT task force. Extended report. *Osteoarthritis Cartilage* 2008;16:742-8.
24. Lanyon P, Jones A, Doherty M. Assessing progression of patello femoral osteoarthritis: A comparison between two radiographic methods. *Ann Rheum Di.* 1996;55:875-9.
25. LaValley MP, McLaughlin S, Goggins J, et al. The lateral view radiograph for assessment of the tibiofemoral joint space in knee osteoarthritis: its reliability, sensitivity to change, and longitudinal validity. *Arthritis Rheum* 2005;52:3542-7.
26. Nevitt MC, Peterfy C, Guermazi A, et al. Longitudinal performance evaluation and validation of fixed-flexion radiography of the knee for detection of joint space loss. *Arthritis Rheum* 2007;56:1512-20.
27. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: A randomised, placebo-controlled clinical trial. *Lancet* 2001;357:251-6.
28. Sugiyama S IM, Suzuki Y, Shimizu K. Procollagen II C propeptide level in the synovial fluid as a predictor of radiographic progression in early knee osteoarthritis. *Ann Rheum Dis* 2003;62:27-32.
29. Reichmann WM, Katz JN, Losina E. Differences in self-reported health in the osteoarthritis Initiative (OAI) and Third national health and nutrition Examination survey (NHANES-III). *PloS one* 2011;6.
30. Duryea J, Neumann G, Niu J, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: Analysis of longitudinal data from the osteoarthritis initiative. *Arthritis Care Res* 2010;62:932-7.
31. Eckstein F, Maschek S, Wirth W, et al. One year change of knee cartilage morphology in the first release of participants from the Osteoarthritis Initiative progression subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status. *Ann Rheum DIs* 2009;68:674-9.
32. Eckstein F, Wirth W, Hudelmaier MI, et al. Relationship of compartment-specific structural knee status at baseline with change in cartilage morphology: a prospective observational study using data from the osteoarthritis initiative. *Arthritis Res THer* 2009;11:R90.
33. Eckstein F, Buck RJ, Burstein D, et al. Precision of 3.0 Tesla quantitative magnetic resonance imaging of cartilage morphology in a multicentre clinical trial. *Ann Rheum Dis* 2008;67:1683-8.
34. Eckstein F, Benichou O, Wirth W, et al. Magnetic resonance imaging-based cartilage loss in painful contralateral knees with and without radiographic joint space narrowing: Data from the Osteoarthritis Initiative. *Arthritis Rheum* 2009;61:1218-25.
35. Blumenkrantz G, Lindsey CT, Dunn TC, et al. A pilot, two-year longitudinal study of the interrelationship between trabecular bone and articular cartilage in the osteoarthritic knee. *Osteoarthritis Cartilage* 2004;12:997-1005.
36. Eckstein F, Nevitt M, Gimona A, et al. Rates of change and sensitivity to change in cartilage morphology in healthy knees and in knees with mild, moderate, and end-stage radiographic osteoarthritis: results from 831 participants from the Osteoarthritis Initiative. *Arthritis Care Res* 2011;63:311-9.
37. Hunter DJ, Niu J, Zhang Y, et al. Change in cartilage morphometry: a sample of the progression cohort of the Osteoarthritis Initiative. *Ann Rheum Dis* 2009;68:349-56.
38. Hunter DJ, Li L, Zhang YQ, et al. Region of interest analysis: by selecting regions with denuded areas can we detect greater amounts of change? *Osteoarthritis Cartilage* 2010;18:175-83.
39. Maschek S, Wirth W, Ladel C, et al. Rates and sensitivity of knee cartilage thickness loss in specific central reading radiographic strata from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2014;22:1550-3.
40. Cromer MS, Bourne RM, Fransen M, et al. Responsiveness of quantitative cartilage measures over one year in knee osteoarthritis: comparison of radiography and MRI assessments. *J magne reson imaging* 2014;39:103-9.
41. Buck RJ, Wyman BT, Le Graverand MP, et al. Osteoarthritis may not be a one-way-road of cartilage loss--comparison of spatial patterns of cartilage change between osteoarthritic and healthy knees. *Osteoarthritis Cartilage* 2010;18:329-35.
42. Eckstein F, Kunz M, Schutzer M, et al. Two year longitudinal change and test-retest-precision of knee cartilage morphology in a pilot study for the osteoarthritis initiative. *Osteoarthritis Cartilage* 2007;15:1326-32.
43. Hudelmaier M, Wirth W, Wehr B, et al. Femorotibial cartilage morphology: reproducibility of different metrics and femoral regions, and sensitivity to change in disease. *Cells tissues organs* 2010;192:340-50.
44. Iranpour-Boroujeni T, Watanabe A, Bashtar R, et al. Quantification of cartilage loss in local regions of knee joints using semi-automated segmentation software: analysis of longitudinal data from the Osteoarthritis Initiative (OAI). *Osteoarthritis Cartilage* 2011;19:309-14.
45. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. *Arthritis Rheum* 2004;50:476-87.
46. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, et al. Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with

clinical symptoms and radiographic changes. *Arthritis Res Ther* 2006;8:R21.
47. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, et al. Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. *Ann Rheum Dis* 2008;67:683-8.
48. Raynauld JP, Martel-Pelletier J, Abram F, et al. Analysis of the precision and sensitivity to change of different approaches to assess cartilage loss by quantitative MRI in a longitudinal multicentre clinical trial in patients with knee osteoarthritis. *Arthritis Res Ther* 2008;10:R129.
49. Raynauld JPM, Bias P, Laufer S, et al. Protecitve effects of licofelone, a 5-lipoxygenase and cyclo-oxygenase inhibitor, versus naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI. *Ann Rheum Dis* 2009;68:938-47.
50. Eckstein F, McCulloch CE, Lynch JA, et al. How do short-term rates of femorotibial cartilage change compare to long-term changes? Four year follow-up data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2012;20:1250-7.
51. Amin S, LaValley MP, Guermazi A, et al. The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. *Arthritis Rheum* 2005;52:3152-9.
52. Gandy SJ, Dieppe PA, Keen MC, et al. No loss of cartilage volume over three years in patients with knee osteoarthritis as assessed by magnetic resonance imaging. *Osteoarthritis Cartilage* 2002;10:929-37.
53. Hunter DJ, Zhang Y, Niu J, et al. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum* 2006;54:1529-35.
54. Pelletier JP, Raynauld JP, Abram F, et al. A new non-invasive method to assess synovitis severity in relation to symptoms and cartilage volume loss in knee osteoarthritis patients using MRI. *Osteoarthritis Cartilage* 2008;16 Suppl 3:S8-13.
55. Brandt KD, Mazzuca SA, Buckwalter KA. Acetaminophen, like conventional NSAIDs, may reduce synovitis in osteoarthritic knees. *Rheumatology (Oxford)* 2006;45:1389-94.
56. Hunter DJ, Conaghan PG, Peterfy CG, et al. Responsiveness, effect size, and smallest detectable difference of Magnetic Resonance Imaging in knee osteoarthritis. *Osteoarthritis Cartilage* 2006;14 Suppl A:A112-5.
57. Hunter DJ, Zhang W, Conaghan PG, et al. Responsiveness and reliability of MRI in knee osteoarthritis: a meta-analysis of published evidence. *Osteoarthritis Cartilage* 2011;19:589-605.
58. Stahl R, Blumenkrantz G, Carballido-Gamio J, et al. MRI-derived T2 relaxation times and cartilage morphometry of the tibio-femoral joint in subjects with and without osteoarthritis during a 1-year follow-up. *Osteoarthritis Cartilage* 2007;15:1225-34.
59. Wirth W, Hellio Le Graverand MP, Wyman BT, et al. Regional analysis of femorotibial cartilage loss in a subsample from the Osteoarthritis Initiative progression subcohort. *Osteoarthritis Cartilage* 2009;17:291-7.
60. Wirth W, Buck R, Nevitt M, et al. MRI-based extended ordered values more efficiently differentiate cartilage loss in knees with and without joint space narrowing than region-specific approaches using MRI or radiography--data from the OA initiative. *Osteoarthritis Cartilage* 2011;19:689-99.
61. Wirth W, Benichou O, Kwoh CK, et al. Spatial patterns of cartilage loss in the medial femoral condyle in osteoarthritic knees: data from the Osteoarthritis Initiative. *Magn Reson Med* 2010;63:574-81
62. Creamer P, Sharif M, George E, et al. Intra-articular hyaluronic acid in osteoarthritis of the knee: an investigation into mechanisms of action. *Osteoarthritis Cartilage* 1994;2:133-40.
63. Hall M, Doherty S, Courtney P, et al. Ultrasound detected synovial change and pain response following intra-articular injection of corticosteroid and a placebo in symptomatic osteoarthritic knees: a pilot study. *Ann Reum Dis* 2014;73:1590-1.
64. Song IH, Althoff CE, Hermann KG, et al. Contrast-enhanced ultrasound in monitoring the efficacy of a bradykinin receptor 2 antagonist in painful knee osteoarthritis compared with MRI. *Ann Rheum Dis* 2009;68:75-83.
65. Hall M, Doherty S, Courtney P, et al. Synovial pathology detected on ultrasound correlates with the severity of radiographic knee osteoarthritis more than with symptoms. *Osteoarthritis Cartilage* 2014;22:1627-33
66. Botha-Scheepers S, Riyazi N, Watt I, et al. Progression of hand osteoarthritis over 2 years: A clinical and radiological follow-up study. *Ann Rheum Dis* 2009;68:1260-4
67. Botha-Scheepers S, Watt I, Breedveld FC, et al. Reading radiographs in pairs or in chronological order influences radiological progression in osteoarthritis. *Rheumatology (Oxford)* 2005;44:1452-5.
68. Maheu E, Cadet C, Gueneugues S, et al. Reproducibility and sensitivity to change of four scoring methods for the radiological assessment of osteoarthritis of the hand. *Ann Rheum Dis* 2007;66:464-9.
69. Buckland-Wright JC, Macfarlane DG, Lynch JA. Osteophytes in the osteoarthritic hand: their incidence, size, distribution, and progression. *Ann Rheum Dis* 1991;50:627-30.
70. Auleley GR, Giraudeau B, Dougados M, et al. Radiographic assessment of hip osteoarthritis progression: Impact of reading procedures for longitudinal studies. *Ann Rheum Dis* 2000;59:422-7.

71. Botha-Scheepers S, Watt I, Rosendaal FR, et al. Changes in outcome measures for impairment, activity limitation, and participation restriction over two years in osteoarthritis of the lower extremities. *Arthritis Care Res* 2008;59:1750-5.
72. Conrozier T, Brandt K, Piperno M, et al. Reproducibility and sensitivity to change of a new method of computer measurement of joint space width in hip osteoarthritis. Performance of three radiographic views obtained at a 3-year interval. *Osteoarthritis Cartilage* 2009;17:864-70.
73. Conrozier T, Saxne T, Fan CSS, et al. Serum concentrations of cartilage oligomeric matrix protein and bone sialoprotein in hip osteoarthritis: A one year prospective study. *Ann Rheum Dis* 1998;57:527-32.
74. Dougados M, Nguyen M, Berdah L, et al. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. *Arthritis Rheum* 2001;44:2539-47.
75. Maheu E, Cadet C, Marty M, et al. Reproducibility and sensitivity to change of various methods to measure joint space width in osteoarthritis of the hip: a double reading of three different radiographic views taken with a three-year interval. *Arthritis Res Ther* 2005;7:R1375-85.
76. Maillefert JF, Sharp JT, Aho LS, et al. Comparison of a computer based method and the classical manual method for radiographic joint space width assessment in hip osteoarthritis. *J Rheumatol* 2002;29:2592-6.
77. Papaloucas CD, Ward RJ, Tonkin CJ, et al. Cancellous bone changes in hip osteoarthritis: a short-term longitudinal study using fractal signature analysis. *Osteoarthritis Cartilage* 2005;13:998-1003.
78. Pavelka K, Gatterova J, Gollerova V, et al. A 5-year randomized controlled, double-blind study of glycosaminoglycan polysulphuric acid complex (Rumalon(registered trademark)) as a structure modifying therapy in osteoarthritis of the hip and knee. *Osteoarthritis Cartilage* 2000;8:335-42.
79. Ratzlaff C, Van Wyngaarden C, Duryea J. Location-specific hip joint space width for progression of hip osteoarthritis - Data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2014;22:1481-7.
80. Jaremko JL, Lambert RG, Zubler V, et al. Methodologies for semiquantitative evaluation of hip osteoarthritis by magnetic resonance imaging: approaches based on the whole organ and focused on active lesions. *J Rheumatol* 2014;41:359-69.
81. Conrozier T, Jousseaume CA, Mathieu P, et al. Quantitative measurement of joint space narrowing progression in hip osteoarthritis: A longitudinal retrospective study of patients treated by total hip arthroplasty. *Br J Rheumatol* 1998;37:961-8.
82. Maillefert JF, Gueguen A, Nguyen M, et al. Relevant change in radiological progression in patients with hip osteoarthritis. I. Determination using predictive validity for total hip arthroplasty. *Rheumatology (Oxford)* 2002;41:142-7.
83. Gossec L, Jordan JM, Lam MA, et al. Comparative evaluation of three semi-quantitative radiographic grading techniques for hip osteoarthritis in terms of validity and reproducibility in 1404 radiographs: report of the OARSI-OMERACT Task Force. *Osteoarthritis Cartilage* 2009;17:182-7.
84. Lequesne M, Maheu E, Cadet C, et al. Structural effect of avocado/soybean unsaponifiables on joint space loss in osteoarthritis of the hip. *Arthritis Care Res* 2002;47:50-8.
85. Dougados MGA, Nguyen M, Berdah L, et al. Radiological progression of hip osteoarthritis: definition, risk factors and correlations with clinical status. *Ann Rheum Dis*. 1996;55:356-62.
86. Iagnocco A, Filippucci E, Riente L, et al. Ultrasound imaging for the rheumatologist XLI. Sonographic assessment of the hip in OA patients. *Clin Exp Rheumatol* 2012;30:652-7.
87. Cromer MS, Bourne RM, Fransen M, et al. Responsiveness of quantitative cartilage measures over one year in knee osteoarthritis: comparison of radiography and MRI assessments. *J magne reson imaging* 2014;39:103-9.
88. Felson DT, Parkes MJ, Marjanovic EJ, et al. Bone marrow lesions in knee osteoarthritis change in 6-12 weeks. *Osteoarthritis Cartilage* 2012;20:1514-8.
89. Hunter DJ, Bowes MA, Eaton CB, et al. Can cartilage loss be detected in knee osteoarthritis (OA) patients with 3-6 months' observation using advanced image analysis of 3T MRI *Osteoarthritis Cartilage* 2010;18:677-83.
90. Stahl R, Jain SK, Lutz J, et al. Osteoarthritis of the knee at 3.0 T: comparison of a quantitative and a semi-quantitative score for the assessment of the extent of cartilage lesion and bone marrow edema pattern in a 24-month longitudinal study. *Skeletal Radiol* 2011;40:1315-27
91. Kubota M, Ishijima M, Kurosawa H, et al. A longitudinal study of the relationship between the status of bone marrow abnormalities and progression of knee osteoarthritis. *J Orthop Sci* 2010;15:641-6.
92. Jan MH, Chai HM, Wang CL, et al. Effects of repetitive shortwave diathermy for reducing synovitis in patients with knee osteoarthritis: an ultrasonographic study. *Phys Ther* 2006;86:236-44.
93. Kawaguchi K, Enokida M, Otsuki R, et al. Ultrasonographic evaluation of medial radial displacement of the medial meniscus in knee osteoarthritis. *Arthritis Rheum* 2012;64:173-80.
94. Bijsterbosch J, Haugen IK, Malines C, et al. Reliability, sensitivity to change and feasibility of three radiographic scoring methods for hand osteoarthritis. *Ann Rheum Dis* 2011;70:1465-7.
95. Jans L, De Coninck T, Wittoek R, et al. 3 T DCE-MRI assessment of synovitis of the interphalangeal joints in patients with erosive osteoarthritis for treatment response monitoring. *Skeletal Radiol* 2013;42:255-60.

96. Grainger AJ, Farrant JM, O'Connor PJ, et al. MR imaging of erosions in interphalangeal joint osteoarthritis: is all osteoarthritis erosive? *Skeletal Radiol* 2007;36:737-45.
97. Bartlett SJ, Ling SM, Mayo NE, et al. Identifying common trajectories of joint space narrowing over two years in knee osteoarthritis. *Arthritis Care Res* 2011;63:1722-8.
98. Bruyere O, Genant H, Kothari M, et al. Longitudinal study of magnetic resonance imaging and standard X-rays to assess disease progression in osteoarthritis. *Osteoarthritis Cartilage* 2007;15:98-103.
99. Teichtahl AJ, Wluka AE, Wang Y, et al. Obesity and adiposity are associated with the rate of patella cartilage volume loss over 2 years in adults without knee osteoarthritis. *Ann Rheum Dis* 2009;68:909-13.
100. Teichtahl AJ, Wluka AE, Cicuttini FM. Frontal plane knee alignment is associated with a longitudinal reduction in patella cartilage volume in people with knee osteoarthritis. O *Osteoarthritis Cartilage* 2008;16:851-4.
101. Cicuttini F, Hankin J, Jones G, et al. Comparison of conventional standing knee radiographs and magnetic resonance imaging in assessing progression of tibiofemoral joint osteoarthritis. *Osteoarthritis Cartilage* 2005;13:722-7.
102. Hunter DJ, Zhang Y, Niu J, et al. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum* 2006;54:1529-35.
103. Felson DT, Lynch J, Guermazi A, et al. Comparison of BLOKS and WORMS scoring systems part II. Longitudinal assessment of knee MRIs for osteoarthritis and suggested approach based on their performance: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2010;18:1402-7.
104. Crema MD, Hunter DJ, Burstein D, et al. Association of changes in delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) with changes in cartilage thickness in the medial tibiofemoral compartment of the knee: a 2 year follow-up study using 3.0 T MRI. *Ann Rheum Dis* 2014;73:1935-41.
105. Amin S, LaValley MP, Guermazi A, et al. The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. *Arthritis Rheum* 2005;52:3152-9.
106. Fukui N, Yamane S, Ishida S, et al. Relationship between radiographic changes and symptoms or physical examination findings in subjects with symptomatic medial knee osteoarthritis: A three-year prospective study. *BMC musculoskelet disord* 2010;11
107. Eckstein F, Boudreau RM, Wang Z, et al. Trajectory of cartilage loss within 4 years of knee replacement - a nested case-control study from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2014;22:1542-9.
108. Kornaat PR, Kloppenburg M, Sharma R, et al. Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis; associations with clinical features. *Eur Radiol* 2007;17:3073-8.
109. Phan CM, Link TM, Blumenkrantz G, et al. MR imaging findings in the follow-up of patients with different stages of knee osteoarthritis and the correlation with clinical symptoms. *Eur Radiol* 2006;16:608-18.
110. Zhang Y, Nevitt M, Niu J, et al. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arthritis Rheum* 2011;63:691-9.
111. Haugen IK, Slatkowsky-Christensen B, Boyesen P, et al. Cross-sectional and longitudinal associations between radiographic features and measures of pain and physical function in hand osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1191-8.
112. Haugen IK, Boyesen P, van der Heijde D, et al. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. *Arthritis Rheum* 2014;66(S10).
113. Bandinelli F, Fedi R, Generini S, et al. Longitudinal ultrasound and clinical follow-up of Baker's cysts injection with steroids in knee osteoarthritis. *Clin Rheumatol* 2012;31:727-31.
114. Keen HI, Wakefield RJ, Hensor EMA, et al. Response of symptoms and synovitis to intra-muscular methylprednisolone in osteoarthritis of the hand: An ultrasonographic study. *Rheumatology (Oxford)* 2010;49:1093-100.
115. Klauser AS, Kupferthaler K, Feuchtner G, et al. Sonographic criteria for therapy follow-up in the course of ultrasound-guided intra-articular injections of hyaluronic acid in hand osteoarthritis. *Eur J Radiol* 2012;81:1607-11.
116. Brealey SD. Influence of magnetic resonance imaging of the knee on GPs' decisions: A randomised trial. *Br J Gen Pract* 2007;57:622-9.
117. Ritchie JF, Al-Sarawan M, Worth R, et al. A parallel approach: the impact of schuss radiography of the degenerate knee on clinical management. *Knee* 2004;11:283-7.
118. Dolin SJ, De CWAC, Ashford N, et al. Factors affecting medical decision-making in patients with osteoarthritis of the hip: Allocation of surgical priority. *Disabil and Rehabil* 2003;25:771-7.
119. Bhattacharya R, Kumar V, Safawi E, et al. The knee skyline radiograph: its usefulness in the diagnosis of patello-femoral osteoarthritis. *Int Orthop* 2007;31:247-52.
120. Chang CB, Seong SC, Kim TK. Evaluations of radiographic joint space - do they adequately predict cartilage conditions in the patellofemoral joint of the patients undergoing total knee arthroplasty for advanced knee osteoarthritis? *Osteoarthritis Cartilage* 2008;16:1160-6.

121. Dervin GF, Feibel RJ, Rody K, et al. 3-Foot standing AP versus 45 degrees PA radiograph for osteoarthritis of the knee. *Clin J Sport Med* 2001;11:10-6.
122. Waldstein W, Monsef JB, Buckup J, et al. The value of valgus stress radiographs in the workup for medial unicompartmental arthritis knee. *Clin orthoped Rel Res* 2013;471:3998-4003.
123. De Lange-Brokaar BJE, Ioan-Facsinay A, Yusuf E, et al. Degree of synovitis on MRI by comprehensive whole knee semi-quantitative scoring method correlates with histologic and macroscopic features of synovial tissue inflammation in knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22:1606-13.
124. Fernandez-Madrid F, Karvonen RL, Teitge RA, et al. Synovial thickening detected by MR imaging in osteoarthritis of the knee confirmed by biopsy as synovitis. *Magn reson imaging* 1995;13:177-83.
125. Bergman AG, Willen HK, Lindstrand AL, et al. Osteoarthritis of the knee: correlation of subchondral MR signal abnormalities with histopathologic and radiographic features. *Skeletal Radiol* 1994;23:445-8.
126. Broderick LS, Turner DA, Renfrew DL, et al. Severity of articular cartilage abnormality in patients with osteoarthritis: evaluation with fast spin-echo MR vs arthroscopy. *AJR Am J Roentgen* 1994;162:99-103.
127. Kalunian KC, Arnold WJ, Klashman DJ, et al. Can physical signs or magnetic resonance imaging substitute for diagnostic arthroscopy in knee osteoarthritis patients with suspected internal derangements? A pilot study. *J Clin Rheumatol* 2000;6:123-7.
128. Loeuille D, Sauliere N, Champigneulle J, et al. Comparing non-enhanced and enhanced sequences in the assessment of effusion and synovitis in knee OA: associations with clinical, macroscopic and microscopic features. *Osteoarthritis Cartilage* 2011;19:1433-9.
129. Saadat E, Jobke B, Chu B, et al. Diagnostic performance of in vivo 3-T MRI for articular cartilage abnormalities in human osteoarthritic knees using histology as standard of reference. *Eur Radiol* 2008;18(10):2292-302.
130. Takayama Y, Hatakenaka M, Tsushima H, et al. T1rho is superior to T2 mapping for the evaluation of articular cartilage denaturalization with osteoarthritis: radiological-pathological correlation after total knee arthroplasty. *Eur J Radiol* 2013;82:e192-8.
131. von Engelhardt LV, Lahner M, Klussmann A, et al. Arthroscopy vs. MRI for a detailed assessment of cartilage disease in osteoarthritis: diagnostic value of MRI in clinical practice. *BMC musculoskelet disord* 2010;11:75
132. Wong CS, Yan CH, Gong NJ, et al. Imaging biomarker with T1rho and T2 mappings in osteoarthritis - in vivo human articular cartilage study. *Eur J Radiol* 2013;82:647-50.
133. Yoshioka H, Stevens K, Hargreaves BA, et al. Magnetic resonance imaging of articular cartilage of the knee: Comparison between fat-suppressed three-dimensional SPGR imaging, fat-suppressed FSE imaging, and fat-suppressed three-dimensional DEFT imaging, and correlation with arthroscopy. *J Magn Reson Imaging* 2004;20:857-64.
134. Zanetti M, Bruder E, Romero J, et al. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. *Radiology* 2000;215:835-40.
135. Graichen H, von Eisenhart-Rothe R, Vogl T, et al. Quantitative assessment of cartilage status in osteoarthritis by quantitative magnetic resonance imaging: technical validation for use in analysis of cartilage volume and further morphologic parameters. *Arthritis Rheum* 2004;50:811-6.
136. Moon JS, Lee K, Lee HS, et al. Cartilage lesions in anterior bony impingement of the ankle. *Arthroscopy* 2010;26:984-9.
137. Tol JL, Verhagen RAW, Krips R, et al. The anterior ankle impingement syndrome: Diagnostic value of oblique radiographs. *Foot Ankle Int* 2004;25:63-8.
138. Haims AH, Schweitzer ME, Morrison WB, et al. MRI in the diagnosis of cartilage injury in the wrist. *Am J Roentgenol* 2004;182:1267-70.
139. Taljanovic MS, Graham AR, Benjamin JB, et al. Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. *Skeletal Radiol* 2008;37:423-31.
140. Xu L, Hayashi D, Guermazi A, et al. The diagnostic performance of radiography for detection of osteoarthritis-associated features compared with MRI in hip joints with chronic pain. *Skeletal Radio* 2013;42:1421-8.
141. Chaisson CE, Gale DR, Gale E, et al. Detecting radiographic knee osteoarthritis: what combination of views is optimal? *Rheumatology (Oxford)* 2000;39:1218-21.
142. Cline GA, Meyer JM, Stevens R, et al. Comparison of fixed flexion, fluoroscopic semi-flexed and MTP radiographic methods for obtaining the minimum medial joint space width of the knee in longitudinal osteoarthritis trials. *Osteoarthritis Cartilage* 2006;14 Suppl A:A32-6.
143. Eriksson K, Sadr-Azodi O, Singh C, et al. Stress radiography for osteoarthritis of the knee: a new technique. *Knee surg sports traumatol arthrosc* 2010;18:1356-9.
144. Hellio Le Graverand MP, Vignon EP, Brandt KD, et al. Head-to-head comparison of the Lyon Schuss and fixed flexion radiographic techniques. Long-term reproducibility in normal knees and sensitivity to change in osteoarthritic knees. *Ann Rheum Dis* 2008;67:1562-6.
145. Hing C, Raleigh E, Bailey M, et al. A prospective study of the diagnostic potential of the knee tunnel view

radiograph in assessing anterior knee pain. *Knee* 2007;14:29-33.
146. Lanyon P, O'Reilly S, Jones A, et al. Radiographic assessment of symptomatic knee osteoarthritis in the community: Definitions and normal joint space. *Ann Rheum Dis* 1998;57:595-601.
147. LaValley MP, McLaughlin S, Goggins J, et al. The lateral view radiograph for assessment of the tibiofemoral joint space in knee osteoarthritis: its reliability, sensitivity to change, and longitudinal validity. *Arthritis Rheum* 2005;52:3542-7.
148. Hellio Le Graverand MP, Mazzuca S, Lassere M, et al. Assessment of the radioanatomic positioning of the osteoarthritic knee in serial radiographs: comparison of three acquisition techniques. *Osteoarthritis Cartilage* 2006;14(SUPPL. 1):37-43.
149. Mazzuca SA, Brandt KD, Buckwalter KA. Detection of radiographic joint space narrowing in subjects with knee osteoarthritis: Longitudinal comparison of the metatarsophalangeal and semiflexed anteroposterior views. *Arthritis Rheum* 2003;48:385-90.
150. Mazzuca SA, Hellio Le Graverand MP, Vignon E, et al. Performance of a non-fluoroscopically assisted substitute for the Lyon schuss knee radiograph: quality and reproducibility of positioning and sensitivity to joint space narrowing in osteoarthritic knees. *Osteoarthritis Cartilage* 2008;16:1555-9.
151. Merle-Vincent F, Vignon E, Brandt K, et al. Superiority of the Lyon schuss view over the standing anteroposterior view for detecting joint space narrowing, especially in the lateral tibiofemoral compartment, in early knee osteoarthritis. *Ann Rheum Dis* 2007;66:747-53.
152. Nelson AE, Renner JB, Shi XA, et al. Cross-sectional comparison of extended anteroposterior and posteroanterior fixed flexion positioning to assess radiographic osteoarthritis at the knee: The Johnston County Osteoarthritis Project. *Arthritis Care Res* 2010;62:1342-5.
153. Piperno M, Hellio Le Graverand MP, Conrozier T, et al. Quantitative evaluation of joint space width in femorotibial osteoarthritis: comparison of three radiographic views. *Osteoarthritis Cartilage* 1998;6:252-9.
154. Takahashi T, Yamanaka N, Ikeuchi M, et al. Reproducibility of joint space width and the intermargin distance measurements in patients with medial osteoarthritis of the knee in various degrees of flexion. *Skeletal Radiol* 2009;38:37-42.
155. Waldstein W, Monsef JB, Buckup J, et al. The value of valgus stress radiographs in the workup for medial unicompartmental arthritis knee. *Clin Orthop Rel Res* 2013;471:3998-4003.
156. Wolfe F, Lane NE, Buckland-Wright C. Radiographic methods in knee osteoarthritis: a further comparison of semiflexed (MTP), schuss-tunnel, and weight-bearing anteroposterior views for joint space narrowing and osteophytes. *J Rheumatol* 2002;29:2597-601.
157. Buckland-Wright JC, MacFarlane DG, Jasani MK, et al. Quantitative microfocal radiographic assessment of osteoarthritis of the knee from weight bearing tunnel and semiflexed standing views. *J Rheumatol* 1994;21:1734-41.
158. Buckland-Wright JC, Wolfe F, Ward RJ, et al. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. *J Rheumatol* 1999;26:2664-74.
159. Buckland-Wright JC, Macfarlane DG, Williams SA, et al. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. *Ann Rheum Dis* 1995;54:872-80.
160. Cicuttini FM, Baker J, Hart DJ, et al. Association of pain with radiological changes in different compartments and views of the knee joint. *Osteoarthritis Cartilage* 1996;4:143-7.
161. Jones AC, Ledingham J, McAlindon T, et al. Radiographic assessment of patellofemoral osteoarthritis. *Ann Rheum Dis* 1993;52:655-8.
162. McDonnell SM, Bottomley NJ, Hollinghurst D, et al. Skyline patellofemoral radiographs can only exclude late stage degenerative changes. *Knee* 2011;18:21-3.
163. Auleley GR, Rousselin B, Ayral X, et al. Osteoarthritis of the hip: agreement between joint space width measurements on standing and supine conventional radiographs. *Ann Rheum Dis* 1998;57:519-23.
164. Conrozier T, Lequesne MG, Tron AM, et al. The effects of position on the radiographic joint space in osteoarthritis of the hip. *Osteoarthritis Cartilage* 1997;5:17-22.
165. Pessis E, Chevrot A, Drape JL, et al. Study of the joint space of the hip on supine and weight-bearing digital radiographs. *Clin Radiol* 1999;54:528-32.
166. Maheu E, Cadet C, Marty M, et al. Reproducibility and sensitivity to change of various methods to measure joint space width in osteoarthritis of the hip: a double reading of three different radiographic views taken with a three-year interval. *Arthritis Res Ther* 2005;7:R1375-85.
167. Conrozier T, Brandt K, Piperno M, et al. Reproducibility and sensitivity to change of a new method of computer measurement of joint space width in hip osteoarthritis. Performance of three radiographic views obtained at a 3-year interval. *Osteoarthritis Cartilage* 2009;17:850-6.
168. Roubille C M-PJ, Abram F, Dorais M, et al. Insight into the role of meniscal extrusion and bone marrow lesions in knee osteoarthritis progression and their impact on response to strontium ranleate treatment in a subset

of patients from the SEKOIA study. *Ann Rheum Dis*. 2014;73 (suppl 2):745
169. Barrett JP, Rashkoff E, Sirna EC, et al. Correlation of roentgenographic patterns and clinical manifestations of symptomatic idiopathic osteoarthritis of the knee. *Clin Orthop Rel Res* 1990(253):179-83.
170. Gudbergsen H, Boesen M, Lohmander LS, et al. Weight loss is effective for symptomatic relief in obese subjects with knee osteoarthritis independently of joint damage severity assessed by high-field MRI and radiography. *Osteoarthritis Cartilage* 2012;20:495-502.
171. Gudbergsen H, Boesen M, Christensen R, et al. Radiographs and low field MRI (0.2T) as predictors of efficacy in a weight loss trial in obese women with knee osteoarthritis. *BMC musculoskeletl disord* 2011;12:56.
172. Hellio le Graverand MP, Clemmer RS, Redifer P, et al. A 2-year randomised, double-blind, placebo-controlled, multicentre study of oral selective iNOS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. *Ann Rheum Dis* 2013;72:187-95.
173. Case JP, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: A randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003;163:169-78.
174. Sawitzke AD, Shi H, Finco MF, et al. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: A report from the glucosamine/chondroitin arthritis intervention trial. Arthritis Rheum 2008;58:3183-91.
175. Mazzuca SA, Brandt KD, Chakr R, et al. Varus malalignment negates the structure-modifying benefits of doxycycline in obese women with knee osteoarthritis. *Osteoarthritis Cartilage* 2010;18:1008-11.
176. Toh EM, Prasad PS, Teanby D. Correlating the efficacy of knee viscosupplementation with osteoarthritic changes on roentgenological examination. *Knee* 2002;9:321-30.
177. Chao J, Wu C, Sun B, et al. Inflammatory characteristics on ultrasound predict poorer longterm response to intraarticular corticosteroid injections in knee osteoarthritis. *J Rheumatol* 2010;37:650-5.
178. Pelletier JP RC, Abram F, Delorme P, et al. Impact of meniscal extrusion on the progression of knee osteoarthritis structural changes and the effects of treatment: data from the oateoarthritis initiative progression cohort. *Ann Rheum Dis* 2014;73: 258.
179. Anandacoomarasamy A, Bagga H, Ding C, et al. Predictors of clinical response to intraarticular hylan injections - A prospective study using synovial fluid measures, clinical outcomes, and magnetic resonance imaging. *J Rheumatol* 2008;35:685-90.
180. Knoop J, Dekker J, van der Leeden M, et al. Is the severity of knee osteoarthritis on magnetic resonance imaging associated with outcome of exercise therapy? *Arthritis Care Res*. 2014;66:63-8.
181. Han SH, Park DY, Kim TH. Prognostic factors after intra-articular hyaluronic acid injection in ankle osteoarthritis. *Yonsei Med J* 2014;55:1080-6.
182. Sun SF, Hsu CW, Sun HP, et al. The effect of three weekly intra-articular injections of hyaluronate on pain, function, and balance in patients with unilateral ankle arthritis. *Journal of Bone and Joint Surgery - Series A* 2011;93:1720-6.
183. Mallinson PI, Tun JK, Farnell RD, et al. Osteoarthritis of the thumb carpometacarpal joint: correlation of ultrasound appearances to disability and treatment response. *Clin Radiol* 2013;68:461-5.
184. Wenham CY, Hensor EM, Grainger AJ, et al. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology (Oxford*) 2012;51:2286-94.
185. Atchia I, Kane D, Reed MR, et al. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. *Ann Rheum Dis* 2011;70:110-6.
186. Lequesne M, Maheu E, Cadet C, et al. Structural effect of avocado/soybean unsaponifiables on joint space loss in osteoarthritis of the hip. *Arthritis Care Res* 2002;47:50-8.
187. Rennesson-Rey B, Rat AC, Chary-Valckenaere I, et al. Does joint effusion influence the clinical response to a single Hylan GF-20 injection for hip osteoarthritis? *Joint Bone Spine* 2008;75:182-8.
188. Rozendaal RM, Uitterlinden EJ, van Osch GJVM, et al. Effect of glucosamine sulphate on joint space narrowing, pain and function in patients with hip osteoarthritis; subgroup analyses of a randomized controlled trial. *Osteoarthritis Cartilage* 2009;17:427-32.
189. Hoeksma HL DJ, Ronday HK, Breedveld FC, et al. Manual therapy in osteoarthritis of the hip: outcome in subgroups of patients. *Rheumatology (Oxford)* 2005;44:461-4.
190. Deshmukh AJ, Panagopoulos G, Alizadeh A, et al. Intra-articular hip injection: does pain relief correlate with radiographic severity of osteoarthritis? *Skeletal Radiol* 2011;40:1449-54.
191. van Middelkoop MAN, Atchia I, Birrell F, Chet al. The OA trial bank: meta-analysis of individual patient data show that patients with severe pain or with inflammatory signs detected by ultrasound especially benefit from intra-articular glucocorticoids for knee or hip. *Ann Rheumatic Dis* 2014;73:749-50..
192. Robinson P, Keenan AM, Conaghan PG. Clinical effectiveness and dose response of image-guided intra-articular corticosteroid injection for hip osteoarthritis. *Rheumatology (Oxford)* 2007;46:285-91.
193. Pendleton A, Millar A, O'Kane D, et al. Can sonography be used to predict the response to intra-articular

corticosteroid injection in primary osteoarthritis of the knee? *Scandinavian J Rheumatol* 2008;37:395-7.
194. Hirsch G, Kitas G, Klocke R. Intra-articular corticosteroid injection in osteoarthritis of the knee and hip: factors predicting pain relief--a systematic review. *Semin Arthritis Rheu*. 2013;42:451-73.
195. Im SH, Lee SC, Park YB, et al. Feasibility of sonography for intra-articular injections in the knee through a medial patellar portal. *J Ultrasound Med* 2009;28:1465-70.
196. Jang SH, Lee SC, Lee JH, et al. Comparison of ultrasound (US)-guided intra-articular injections by in-plain and out-of-plain on medial portal of the knee. Rheumatol Int 2013;33:1951-9.
197. Sibbitt Jr WL, Band PA, Kettwich LG, et al. A randomized controlled trial evaluating the cost-effectiveness of sonographic guidance for intra-articular injection of the osteoarthritic knee. *J Clin Rheumatol* 2011;17:409-15.
198. Karalezli N, Ogun TC, Kartal S, et al. The pain associated with intraarticular hyaluronic acid injections for trapeziometacarpal osteoarthritis. *Clin Rheumatol* 2007;26:569-71.
199. Maricar N, Parkes MJ, Callaghan MJ, et al. Where and how to inject the knee--a systematic review. *Semin Arthritis Rheum* 2013;43:195-203.
200. Cunnington J, Marshall N, Hide G, et al. A randomized, double-blind, controlled study of ultrasound-guided corticosteroid injection into the joint of patients with inflammatory arthritis. *Arthritis Rheum* 2010;62:1862-9.
201. Curtiss HM, Finnoff JT, Peck E, et al. Accuracy of ultrasound-guided and palpation-guided knee injections by an experienced and less-experienced injector using a superolateral approach: a cadaveric study. *PMR* 2011;3:507-15.
202. Luz KR, Furtado RN, Nunes CC, et al. Ultrasound-guided intra-articular injections in the wrist in patients with rheumatoid arthritis: a double-blind, randomised controlled study. *Ann Rheum Dis* 2008;67:1198-200.
203. Sibbitt WL, Peisajovich A, Michael AA, et al. Does sonographic needle guidance affect the clinical outcome of intraarticular injections? *J Rheumatol* 2009;36:1892-902.
204. Balint PV, Kane D, Hunter J, et al. Ultrasound guided versus conventional joint and soft tissue fluid aspiration in rheumatology practice: a pilot study. *J Rheumatol* 2002;29:2209-13.