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Perspectives: The role of radiography and MRI in determining patient eligibility for clinical DMOAD trials of knee osteoarthritis

Frank W. Roemer^{†,‡,*}, C. Kent Kwok[§], Daichi Hayashi^{‡,¶}, David T. Felson^{**}, and Ali Guermazi[‡]

[†]Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany

[‡]Quantitative Imaging Center (QIC), Department of Radiology, Boston University School of Medicine, Boston, MA, USA

[§]University of Arizona Arthritis Center & Division of Rheumatology, University of Arizona College of Medicine, Tucson, AZ, USA

[¶]Department of Radiology, Stony Brook Medicine, Stony Brook, NY, United States

^{**}Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, USA

Abstract

Currently no disease-modifying drugs for osteoarthritis have been approved. There are several reasons for failure of clinical trials in the past, including the commonly applied definition of structural eligibility based on radiographic assessment. In the context of precision medicine it will be of increasing relevance to find the appropriate patient for a specific treatment approach. Phenotypical stratification by imaging at eligibility will be paramount in the future and cannot be achieved using radiography alone. Furthermore, joints at high risk for faster progression need to be identified, as these may allow a more efficient DMOAD trial design. In addition, joints at high risk for collapse need to be excluded at screening. MRI may be able to offer solutions in this context, and commonly perceived hurdles in the application of MRI at eligibility assessment are being addressed as a result of technological advances and simplified image assessment.

Introduction

Although a number of potential disease-modifying pharmacological compounds have been investigated in recent years (including but not limited to inducible nitric oxide synthase (iNOS), strontium ranelate, Calcitonin, Matrix metalloproteinase (MMP) inhibitors, Cathepsin K inhibitors and bisphosphonates)^{1–4}, there is still no pharmacological agent that

*Corresponding author and reprint requests: Frank W. Roemer, M.D., froemer@bu.edu.

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has been approved by regulatory agencies as a disease-modifying osteoarthritis (OA) drug (DMOAD). The recently published numbers citing the costs of developing a prescription drug that gains market approval at \$2.6 billion, a 145% cost increase since 2003, and the series of disappointing terminations of late-stage drug development programs all suggest the need for careful reconsideration of the development process for these types of drugs ⁵. The most efficacious compound will only work if administered to appropriate patients who would be responsive to a defined treatment target.

Currently, recruitment of subjects in DMOAD trials is dependent on radiographic structural disease severity as defined by the Kellgren & Lawrence (KL) scale ⁶. Knees with KL grade 0 or 1 are considered not to have structural OA, and thus, are excluded from participating in DMOAD trials, whereas knees with evidence of definite osteophytes (i.e. KL grade 2) or joint space narrowing (i.e. KL grade 3) are considered to have radiographic OA and, thus, are potentially eligible. Commonly, knees exhibiting KL grade 4, i.e. “end-stage disease” with bone-on-bone appearance on the anterior-posterior (AP) radiograph with complete loss of joint space, are also excluded from participating in DMOAD trials due to potential ceiling effects, i.e. no further radiographic progression being possible ⁷.

However, as evidenced in a recent population-based observational study reporting presence of MRI-detected osteophytes in 74% of knees with normal radiographs (i.e. KL grade 0), radiography lacks sensitivity not only for the detection of additional features of OA such as soft tissue changes due to its insufficient soft tissue contrast, but also for visualization of specific bony features of OA such as osteophytes and is not able to visualize cartilage directly ⁸. Cartilage damage is considered as one of the hallmarks of OA. Other pathologic features of OA that are not visualized by radiography and are considered to be associated with pain include subchondral bone marrow lesions (BMLs), synovitis, joint effusion, periarticular cystic lesions and meniscal tears ⁹. In the same study focusing on knees without radiographic OA, a prevalence of BMLs, meniscal tears, and synovitis or effusion as high as 52%, 24%, and 36% was reported ^{8, 10}. These numbers imply that knees with KL grade 0 or 1 should not automatically be considered 'structurally normal' and could be considered for inclusion in OA clinical trials.

A joint contains many different tissues that may exhibit pathologic changes, resulting in many potential targets for treatment. Because of this heterogeneity, it is unlikely that there will be a single treatment for OA that will be similarly efficacious for all types of structural OA. Researchers are increasingly suggesting that there are several phenotypes or subpopulations in OA based on their pathophysiology and structural manifestation of disease ^{11–13}. These may include phenotypes that are characterized by distinct clinical manifestations of disease, by certain laboratory parameters, biochemical markers, and/or imaging criteria ¹⁴. We hypothesize that refocusing on the starting point of any DMOAD trial, i.e. the eligibility criteria, may potentially enhance the likelihood of achieving the desired goal – a treatment that ultimately prevents or delays the structural progression of OA. Using this perspective, we will describe some of the current problems that particularly impact eligibility criteria for knee OA trials from an imaging stand point, and will provide rationale as to why it may be time for a shift from radiography to magnetic resonance imaging (MRI) as the primary imaging modality for defining eligibility criteria, which

would allow the characterization of different structural phenotypes of knee OA based on MRI.

Why radiography is insufficient

We believe that there are several reasons why inclusion of patients into clinical trials based on radiographic assessment to define structural disease is insufficient or even misleading.

Definition of disease severity is insufficient

The first reason is the radiography-based definition of disease severity. As was discussed above, so called “radiographically normal” knees exhibit a spectrum of tissue pathology as shown by MRI and thus cannot necessarily be considered structurally ‘normal’^{8, 10} (**Figure 1**). Variations in knee positioning significantly influence assessment of most radiographic characteristics of OA. This seems to be relevant for semi-quantitative as well as quantitative evaluation, as shown in an exemplary fashion in the Dutch CHECK cohort in which systematic variation in semi-flexed knee joint positioning during image acquisition influenced the measurement of several radiographic parameters including joint space width, which may lead to false-positive or false-negative misclassification in regard to joint space narrowing as shown in **Figure 2**¹⁵.

Associations of radiographic structural damage with pain are weak

Secondly, associations between radiography-depicted structural changes and pain are weak. In population-based studies, a significant discordance between radiographically diagnosed OA and knee pain has been reported^{16, 17}. Whilst radiographic evidence of joint damage predisposes to joint pain, the underlying pathologies leading to pain cannot be readily discerned from radiography alone and may require consideration of other factors (**Figure 3**)¹⁸. Novel study designs are one approach to dealing with this so-called structure-symptom discordance. For example, when inter-individual differences influencing the pain experience (including genetics, sensitization, mood, coping, catastrophizing, and the social context, among others) were adequately accounted for, a strong relationship between radiographic OA and knee pain was observed¹⁹. Despite radiography being the most widely used first-line imaging modality for structural OA evaluation, its inherent limitations should be noted, primarily its lack of ability to directly visualize the majority of OA-related pathological features in and around the joint that are potentially responsible for symptoms related to the disease. Utilizing MRI, several structural alterations such as meniscal tears, subchondral BMLs, subarticular bone attrition, synovitis and effusion have been associated with knee pain^{20–22}. Furthermore, changes in BMLs and inflammatory markers on MRI such as effusion-synovitis and Hoffa-synovitis, two features commonly assessed on non-enhanced MRI as surrogates for whole knee inflammatory activation, are associated with fluctuations in pain in patients with knee OA²³. How much of the variance in pain is accounted for by structural change is not fully understood. One reason for this difficulty may be that most studies that looked at associations of pain with structure have focused on late disease stages when numerous pathologic changes are already commonly present.

OA has many faces not visualized by radiography

Thirdly, OA has different structural phenotypes that cannot be adequately characterized by X-ray¹³. DMOAD efficacy may be most efficiently investigated in patients at risk for more rapid disease progression due to the limitations in trial duration, and researchers are working to better understand which joints are at potential risk for such an accelerated disease evolution that may be labeled as a “fast progressor”-phenotype²⁴⁻²⁵. By including knees with baseline meniscal extrusion and prevalent meniscal structural damage, BMLs and prevalent cartilage lesions, a subpopulation at high risk of progressive cartilage loss in a short time interval may be identified. For patello-femoral disease, joint effusion seems to play an important role for future cartilage loss in a short period of time. In the MOST study, we were able to show that in subjects with no or early structural OA, risk for more rapid disease progression was increased for those with prevalent meniscal damage, meniscal extrusion, and any high-grade MRI feature²⁷. Baseline synovitis and effusion and higher BMI score further increased the risk of fast cartilage loss²⁷. Additional proposed structural phenotypes include an inflammatory/synovial phenotype, a bone phenotype characterized by marked subchondral bone changes, a meniscal phenotype leading to altered biomechanics and subsequent cartilage loss, and phenotypes characterized by presence or absence of osteophyte formation, (i.e. hypertrophic or atrophic phenotypes, respectively)^{13, 28, 29}. Of the above phenotypes described, only the latter two may adequately be characterized by radiography.

Radiography does not depict diagnoses of exclusion

Finally, radiography is not able to detect some potentially detrimental findings that may increase risk for joint collapse or fast progression regardless of potential DMOAD treatment. These include but are not limited to findings that are only visible on MRI and may lead to marked alterations in biomechanics and/or perfusion and eventual collapse and disintegration of the articular surface. These entities include subchondral insufficiency fracture, osteonecrosis, meniscal root tears, malignant bone marrow infiltration and synovial tumors (such as PVNS) that – if not treated adequately – may lead to joint collapse as manifested by disintegration of the articular surface and subsequent structural deterioration including depression of the articular surface and dislocation of osteochondral fragments^{30, 31}. While overall these entities are considered as rare, there are no specific prevalence estimates available. Joints with these diagnoses are commonly included in epidemiologic and clinical studies. For example, based on a retrospective institutional database free-text search 84 cases of medial or lateral femoral condyle subchondral insufficiency fracture were described for a 13 year period³².

Why MRI may offer solutions

MRI enables OA researchers to overcome some of the described obstacles as it offers a tomographic viewing perspective unlike radiography, which is a projectional two-dimensional technique³³. MRI can depict all joint tissues and thus will enable a more expansive phenotypic characterization, including tissues that may be responsible for the pain experience in OA³⁴. Finally, MRI is able to screen for subjects at risk for a non-favorable adverse event. However, up to now MRI has been perceived as a tool that is too complex and

expensive to be applied in large scale endeavors such as in eligibility screening for clinical DMOAD trials. As such, radiography is still the commonly used imaging method for defining structural eligibility. We will provide a rationale to support the revision of this paradigm. There are several technological advances that support this argument and these key points are summarized in Box 1.

Advances in image acquisition

While MRI has been clinically applied for more than 30 years with a very low risk profile when contraindications are carefully considered (e.g., cardiac pacemakers), current acquisition of a knee joint MRI is still relatively time consuming in comparison to radiography. This may be one reason for MRI being perceived as not feasible for large scale screening efforts today. Other limitations of MRI include associated costs, the fact that only one single joint can be imaged at a time, limits regarding obese patients (most scanners are limited to a maximum weight of 180 kg), exclusion of patients with cardiac pacemakers or detection of incidental findings of unknown clinical relevance. Advances in imaging technology have enabled marked acceleration of image acquisition that may potentially reduce imaging time to a fraction of previous acquisition times, however, and as a consequence will improve feasibility and lower associated costs significantly. These include technical advances like parallel imaging or improvements in 3D fast spin echo imaging that now allow for acquisition of triplanar MRI of the knee with fat-suppressed fluid sensitive contrast in less than 5 min^{35–37}. These methodologic advances may potentially be applied to large knee OA screening endeavors with markedly reduced image acquisition time and costs³⁸.

Simplified image assessment

Another challenge of using MRI as a screening tool today is that the current assessment tools focus on multi-tissue involvement of OA. Current semiquantitative (SQ) multi-tissue approaches are labor-intensive and challenging to apply in a screening setting to define inclusion into a clinical trial, as several thousands of subjects may need to be screened to determine eligibility.

Current semiquantitative scoring systems include assessment of several pathological features of OA including BMLs, subchondral cysts, articular cartilage, osteophytes, Hoffa-synovitis and effusion-synovitis, meniscus, tendons and ligaments, and periarticular features such as cysts and bursitides^{39–41}.^{42–43}

The aim of any MRI screening would be to define subsamples that exhibit specific OA phenotypes most likely to benefit from a given pharmacologic intervention. As an example, the goal for inclusion into a trial of a compound with an anti-inflammatory mechanism of action would be to enrich the trial population with subjects exhibiting an inflammatory phenotype. Such a phenotype could be defined by MRI as having a high prevalence of synovitis, joint effusion or potentially BMLs. In addition, inclusion of subjects that are more likely to progress faster than others would be desirable given the limited duration of clinical trials. In order to achieve such phenotypic characterization in a screening effort, no elaborate whole organ assessment would be needed. Instead, a simplified instrument could be utilized,

using a tri-compartmental anatomic approach to define the compartment(s) most affected and then applying a simplified assessment that targets the mechanism of action of the DMOAD under study -- including measures of BML, meniscus, cartilage, osteophytes and inflammation, as appropriate -- to aid in defining a specific structural phenotype.

MRI allows phenotypic structural stratification

It has been suggested previously that there is an urgent medical need to further identify disease phenotypes, preferably by simple technologies, to allow for patient selection of bone, cartilage and inflammation-driven OA phenotypes, and then matching the best intervention to each individual phenotype^{25, 28}. From a structural MRI-centric perspective, we suggest that it is possible to differentiate five different phenotypes based on the tissue pathologies that are most severely affected by disease. These phenotypes exhibit distinct phenotypic structural characteristics, such as the atrophic or hypertrophic phenotypes, or possess structural characteristics that predispose a joint for faster progression. We clearly acknowledge that this attempt has limitations based on the fact that structural phenotypes are likely overlapping, and more than one may be present in an individual. OA is a heterogeneous disease with different pathways including multiple tissues involved that exhibit structural damage. For this reason we suggest characterizing a 'predominant' structural phenotype. Definition of these phenotypes certainly will need to be refined and novel analytic approaches may help in doing so^{14, 44, 45}. We also wish to emphasize that structural characterization based on imaging findings is only one aspect used to define patient inclusion criteria for clinical trials. Demographic and clinical parameters are similarly relevant and include factors like age, pain, function, BMI, alignment, etc.

An inflammatory phenotype would be defined by marked synovitis and/or joint effusion on MRI. Synovitis in OA is thought to be a secondary phenomenon related to cartilage deterioration, and there is evidence that synovitis also plays a role in progression of cartilage loss in knee OA⁴⁶. Using arthroscopy as a reference standard, Ayril et al. found that 29% of OA knees had a reactive aspect and 21% an inflammatory aspect of the synovium. Interestingly, only the inflammatory synovitis group showed an association with cartilage loss at 1-year follow-up.⁴⁷

The subchondral bone phenotype would be characterized by large BMLs. BMLs are defined on MRI as non-cystic subchondral areas of ill-defined hyperintensity on fluid sensitive fat suppressed MRI sequences that are frequently seen in conjunction with cartilage damage in the same region^{48, 49}. BMLs play an important role in predicting structural progression and fluctuation of symptoms in subjects with knee OA and, thus, have become a treatment target for novel therapeutic approaches^{23, 50, 51}. Knees with large uni-or multi-compartmental BMLs may be defined as a subchondral-phenotype of knee OA.

A meniscal phenotype will exhibit meniscal damage and/or meniscal extrusion on MRI. The meniscus plays a critical protective role in the tibiofemoral compartments due to its shock-absorbing and load-distributing properties. It is rare to find normal meniscal morphology in compartments with OA; instead, the meniscus is often torn, macerated, or even totally destructed, suggesting a strong association between tibiofemoral OA and meniscal pathology⁵². Although extensive radiological literature on different types of meniscal

pathology is available, there is minor emphasis on the relevance of different types of meniscal damage for incident OA and progression of disease⁵³. We know that meniscal pathology plays a role in predicting cartilage loss in the tibiofemoral compartments including meniscal extrusion (**Figure 4**)^{54–56}.

Based on the presence or absence of osteophytes, a hypertrophic or atrophic OA phenotype may also be defined. A cross-sectional study using a population-based cohort and evaluating different phenotypes of knee OA on MRI demonstrated that severe cartilage damage in the knee is commonly associated with large osteophytes²⁹. In contrast, osteophyte formation may lag behind cartilage loss, which might then manifest as an atrophic OA phenotype characterized by no or only tiny osteophytes yet marked cartilage loss. Using a stringent MRI-based definition, such an atrophic knee OA phenotype has exhibited very low prevalence in the general population²⁹. Currently, there is no radiography-based definition of atrophic OA, with this entity usually being understood as a phenotype of OA exhibiting compartments or joints with definite joint space narrowing without any osteophytes or as a marked discordance between JSN and size of associated osteophyte formation. A recent study based within the MOST cohort surprisingly showed that the atrophic phenotype of knee OA was associated with a decreased likelihood of progression of JSN and cartilage loss compared to the non-atrophic knee OA phenotype⁵⁷.

Generally, it is thought that measurable quantitative cartilage loss rarely occurs in less than 6 months, but according to data from the Joints on Glucosamine Study, cartilage loss, as well as development or progression of bone marrow lesions and meniscal extrusion, do occur in this time frame²⁶. Some of these MRI-detected structural changes could be used as structural outcomes. In addition, a high body mass index, meniscal damage, synovitis or effusion, or any severe baseline MRI-depicted lesions are strongly associated with an increased risk of fast cartilage loss over a 30-month period. The presence of any of these MRI-detectable features at baseline can predict rapid cartilage loss later, permitting the selection of a trial population at high risk of disease progression²⁷. While it is not known whether such knees at higher risk for progression would more likely benefit from a pharmacologic intervention compared to others, more efficient trial designs may be developed by including such patients by decreasing overall trial duration.

Thus, depending on the length of a trial, investigators could select subjects with these MRI-based risk factors for preventative or therapeutic OA trials. Examples of the different MRI-defined structural phenotypes are shown in **Figure 5**.

Diagnoses of exclusion

In addition, there are diagnoses that should ideally be excluded at screening as these will not be amenable to a DMOAD but will show a negative outcome regardless of potential treatment of OA with a DMOAD^{11–13}. These include subchondral insufficiency fracture, meniscal root tears, malignant bone marrow infiltration or synovial tumors such as pigmented villo-nodular synovitis¹⁴, which are not covered by current assessment tools and are occult on radiography until very late in the course of the disease. Unfortunately, prevalence data of these entities in a context of OA clinical trials is not available. Subchondral insufficiency fractures (SIF) of the knee are difficult to detect and may have an

unpredictable course due to delayed diagnosis and lack of standard treatment approaches. The prognosis may range from full recovery to rapidly escalating joint destruction ⁵⁸. The outcome of SIFs depends on several factors, including the initial fracture size, patient body mass index, and degree of osteopenia, as well as early diagnosis and initial treatment ⁵⁹. Meniscal root tear is a subtype of radial tears that has recently gained much interest in the field of OA research. The ligamentous meniscal root is an essential anchoring point for normal meniscal function and distribution of axial compressive loads across the tibial plateau. Its rupture results in a compromise of the loading profile in the knee joint due to meniscal extrusion and subsequent increased tibiofemoral contact pressures ^{60–65}. By definition, meniscal root tear is an avulsion injury or radial tear occurring within 1 cm of the bony tibial attachment ^{66–68}. Medial posterior root tears result in severe medial instability of the knee, clinically ⁶⁹, and a greater degree of ipsilateral femoral condyle degeneration compared to other types of meniscal tear ⁷⁰. A retrospective arthroscopic study further showed that medial meniscus posterior root tears were associated with greater degree of meniscal extrusion and more cases of osteonecrosis compared with horizontal tears ⁷¹. It is likely that the altered biomechanics as a result of root tears will over-ride any potential DMOAD effect although there is no evidence in this regard available to date.

Tumors of the knee joint, both benign and malignant, although rare, may be observed as incidental findings in screening efforts. Although initial radiographs may be normal, MRI will enable detailed assessment of bone and soft tissue involvement. Concomitant reactive BMLs can be observed in almost all stages of various tumors. Diffuse infiltration of the bone marrow may be observed in several hematologic and oncologic diseases such as lymphoma, multiple myeloma, and others. On MRI this will be reflected as diffuse marrow alterations with signal characteristics similar to periarticular red marrow ⁴⁸. Different diagnoses of exclusion at eligibility are presented in **Figure 6**.

Limitations

This perspective has focused on MRI as an alternative to radiography to be used in screening efforts for eligibility assessment in clinical trials of knee OA. We believe that the advantages of MRI outweigh the inherent limitations of the technique including costs, examination time and availability and we have provided arguments how these may at least partially be overcome. Other modalities have only been marginally discussed as these likely will not be able to represent an alternative to X-ray for eligibility evaluation with the exception of ultrasound potentially being applied for screening patients for signs of inflammation in trials focusing on anti-inflammatory therapeutic approaches or for characterization of osteophyte presence ^{72–74}. Nuclear medicine techniques like bone scintigraphy or positron emission tomography (PET) do not seem adequate to be applied in large scale endeavors as these imply use of ionizing radiation and pose challenges in regard to logistics (availability of tracers, transport to sites, etc.) ^{75–77}. Computed tomography (CT) is an important and widely available tool sharing some of the shortcomings of X-ray in that it is a X-ray based technique and characterized by low soft tissue contrast but is well suited to visualize bony changes of OA ⁷⁸.

Conclusions

The failure of OA clinical trials of drugs to date may be due, in part, to the failure of radiography-based eligibility criteria. MRI can help investigators select subjects who are most suitable for a specific aim of the trial, taking into account disease phenotypes and potential treatment targets. Recent technical advances leading to accelerated image acquisition and simplified assessment tools could enable MRI to be feasible in a screening effort at eligibility including phenotypic characterization, definition of exclusionary findings (for reasons of safety and limiting of potential adverse events) and definition of joints at high risk for progression. Potential hurdles are costs and access to MRI systems, but we believe that these potential limitations can be overcome with methodologic advances that are in process. This will result in more targeted treatment and will minimize one of the reasons for failure of DMOAD trials, i.e. not including the right patient for the right treatment. All in all, it is time for OA research to break with the practice of depending entirely on radiography to define eligibility in OA clinical trials.

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Box 1: Limitations of radiography and potential solutions**Limitations of radiography**

- Detailed phenotypic structural characterization is not possible using radiography.
- Definition of structural disease severity using radiography is insufficient.
- Radiography is not able to depict exclusionary findings or visualizes these only in advanced stages. Exposes patients to ionizing radiation.
- Use of radiography to include/exclude potential trial participants may be one of the reasons for failure of DMOAD clinical trials.

MRI-based solutions

- Fast image acquisition in 5 minutes or less is possible using modern MRI techniques, thus improving feasibility of MRI and markedly reducing acquisition costs.
- No radiation concerns and only very few contraindications.
- Simplified image assessment tools will enable less costly and timelier eligibility evaluation of MRI datasets.
- MRI allows phenotypic structural stratification into inflammatory, bone, biomechanical (meniscus/cartilage), hypertrophic and atrophic, and fast progression phenotypes.
- MRI, as opposed to radiography, permits early detection of factors that increase the risk of joint collapse (i.e., subchondral insufficiency fracture, osteonecrosis, meniscal root tears, malignant bone marrow infiltration and synovial tumors).
- Joints at high risk for collapse must be excluded from DMOAD trials at screening as a safety issue.

Figure 1.

Radiographically 'normal' knees (i.e. Kellgren & Lawrence Grade 0) are structurally not 'normal'. **A.** Anterior-posterior radiograph of the knee shows a radiographically normal knee without any signs of osteoarthritis (OA). The medial and lateral joint space is not narrowed and there are no osteophytes present. **B.** Corresponding sagittal intermediate-weighted fat-suppressed MRI acquired on the same day shows a large bone marrow lesion in the central subregion of the medial femur (thin white arrows), representing an OA feature that is associated with pain and structural progression. Note additional concomitant MRI features of OA including effusion-synovitis (asterisk) and superficial focal cartilage damage in the central part of the medial femur (thick white arrow).

Figure 2. Positioning. Serial radiographs of the same knee acquired consecutively. **A.** Anterior posterior radiograph of the knee acquired with a positioning frame with 11 degrees flexion shows a normal medial joint space width without signs of narrowing (arrows). **B.** Radiograph of the same knee acquired with 12 degrees flexion shows definite, false positive, decrease in joint space width (arrows). **C.** Radiograph obtained with 13 degrees flexion shows severe, false positive joint space narrowing compared to the image obtained with 11 degrees flexion (arrows). Knee flexion has marked influence on joint space width and may lead to false positive or negative findings particularly in longitudinal studies.

Figure 3.

Differential diagnosis of a painful knee with osteoarthritis. **A.** Anterior-posterior X-ray of a left knee shows marked joint space narrowing laterally (large arrow) and a definite osteophyte at the lateral tibial margin (small arrow) representing Kellgren & Lawrence grade 3 knee osteoarthritis. At the time of the image the patient was complaining about severe lateral joint pain without a history of trauma. **B.** Coronal T1-weighted MRI shows a stress fracture of the lateral tibial plateau (arrows). The knee also shows osteoarthritic features such as lateral tibiofemoral cartilage loss and moderate lateral meniscus extrusion.

Figure 4.

Progression of meniscal extrusion and cartilage damage leading to increase in joint space narrowing on X-ray. **A.** Anterior-posterior radiograph of the knee shows no medial joint space narrowing (arrows) in a patient with previous anterior cruciate ligament repair and bilateral osteoarthritis as characterized by moderate marginal osteophytes at the medial and lateral joint margins. **B.** Follow-up X-ray 2 years later shows marked increase in joint space narrowing medially (arrows). **C.** Corresponding baseline MRI shows a normal medial meniscal body that is aligned with the medial margin of the tibia (arrowhead). There is discrete superficial tibial cartilage damage (arrows). **D.** MRI at 2 years shows marked extrusion of the meniscal body beyond the medial joint margin (arrowheads). In addition,

there is progression of medial cartilage damage (arrows). Joint space narrowing on X-ray may be a result of cartilage damage, meniscal damage or meniscal extrusion, or a combination of these features.

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Figure 5.

Structural phenotypes as defined by MRI. **A.** Atrophic phenotype. Coronal intermediate-weighted fat-suppressed MRI shows marked bone marrow edema at the medial femur (small arrows). In addition there is meniscal extrusion (dashed arrow) and full-thickness cartilage loss at the medial femur (large arrow). No marginal osteophytes are seen at the medial or lateral joint line defining this knee as exhibiting an atrophic phenotype. **B.** Hypertrophic phenotype. Coronal dual echo at steady state (DESS) MRI shows large marginal osteophytes medially and laterally (arrows) characteristic of the hypertrophic phenotype of knee OA. In

addition there are large osteophytes at the femoral notch (arrowheads). In addition there is superficial cartilage damage in the medial and lateral femur and tibia. **C.** Meniscal phenotype. Coronal intermediate-weighted MRI shows diffuse cartilage loss at the medial femur (arrow) and corresponding tibia. In addition there is marked meniscal extrusion beyond the medial joint line (white bars) characteristic for the meniscal phenotype of knee OA. **D.** Coronal DESS MRI of another patient shows only a tiny residuum of the medial meniscal body (large arrow) following extensive partial meniscectomy. There is diffuse cartilage denudation at the medial tibia (small arrows). Furthermore there is a completely missing lateral meniscal body following meniscal resection also on the lateral side (dotted arrow). Note additional cartilage loss at the lateral compartment. Diffuse meniscal damage predisposes the joint for rapid cartilage loss and may be labeled as the meniscal phenotype. **E.** Inflammatory phenotype. Axial DESS MRI shows marked intraarticular joint effusion distending the joint capsule (asterisk). There is superficial cartilage damage at the medial patella facet. **F.** Sagittal intermediate-weighted fat-suppressed MRI of the same knee shows diffuse hyperintensity within Hoffa's fat pad (grade 3 according the MOAKS scoring system), a commonly used imaging surrogate on non contrast-enhanced sequences for whole joint synovitis (arrows). The combination of these MRI findings of joint effusion and Hoffa-synovitis is characteristic of the inflammatory phenotype on MRI.

Figure 6.

Diagnoses of exclusion. **A.** Coronal intermediate-weighted fat-suppressed MRI shows a complete tear of the posterior meniscal root (arrow) leading to marked extrusion of the medial meniscal body beyond the joint line (arrowheads). Meniscal root tear represents a functional meniscectomy and will lead to rapid joint deterioration. **B.** Sagittal intermediate-weighted fat-suppressed MRI in another patient shows a subchondral insufficiency fracture of the medial femoral condyle reflected as a hypointense subchondral line on MRI (thin arrows). There is marked surrounding bone marrow edema (thick arrows). **C.** Sagittal MRI

of the same patient as in **B**, obtained 12 months later show delamination of an osteochondral fragment (blue arrows) that appears to be unstable as shown by fluid between the fragment and the subchondral bone (small white arrow). In addition there are areas of bone marrow edema at the medial femur and tibia (large white arrows). Severe progression of cartilage loss is observed in the weight-bearing aspect of the medial tibia. **D**. Another patient exhibits marked medial joint space narrowing (arrow) and large medial osteophytes defining this knee as Kellgren & Lawrence grade 3. The patient had severe pain at the time of image acquisition. **E**. The corresponding coronal intermediate-weighted fat-suppressed MRI shows a subchondral insufficiency fracture of the medial femur (grey arrow) and marked surrounding bone marrow edema (white arrows). **F**. The follow-up X-ray 6 months later shows no relevant increase in joint space narrowing (arrow) but an unclear radiolucency at the medial femur now also on X-ray suggestive of a subchondral insufficiency fracture (arrowheads). **G**. The corresponding MRI at 6 months follow-up acquired at the same time as the X-ray shows increasing deformity of the articular surface and diffuse concomitant bone marrow edema at the medial femur and tibia (arrows). Note that there is additional marrow reconversion with red bone marrow extending into the distal metaphyseal femur and tibia (asterisk).