

Towards Classification Criteria for Early Osteoarthritis of the Knee

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Abstract

Objective

To propose draft classification criteria for early stage osteoarthritis (OA) of the knee for use in a primary care setting.

Methods

A group of basic scientists, physician-scientists, rheumatologists, orthopedic surgeons and physiotherapists in a workshop setting discussed potential classification criteria for early osteoarthritis of the knee. The workshop was divided into sessions around relevant topics with short state of the art presentations followed by breakout sessions, consensus discussions, and consolidation into a consensus document.

Results

Three classes of criteria were agreed: 1. Pain, symptoms/signs, self-reported function and quality of life using tools such as KOOS: scoring $\leq 85\%$ in at least 2 out of these 4 categories; 2. Clinical examination: at least 1 present out of joint line tenderness or crepitus ; 3. Knee radiographs: Kellgren & Lawrence (KL) grade of 0 or 1. MRI is at present not recommended as an aid to identify or define early OA in routine clinical practice or primary care, in light of the absence of validated consensus criteria and the high population prevalence of structural joint changes detected by this method. Biomarkers may have future utility in early OA classification, but no individual or set of biomarkers is yet robust enough.

Conclusion

Based on our consensus proposal, draft classification criteria for early OA of the knee for use in clinical studies should include patient reported outcomes such as pain and function, together with clinical signs and KL grade 0-I on radiographs.

Keywords

Early Osteoarthritis - Knee - Classification Criteria

Knee osteoarthritis (OA) is the most common joint disease and is associated with significant pain, disability, premature mortality [1] and costs estimated around 1.5-2% of the GDP in western countries [2]. It is a complex, multifactorial disease with many different phenotypes [3]. In part due to this complexity and phenotypic heterogeneity, there are no proven disease modifying drugs approved by the regulatory agencies. However, new treatment targets are being identified, raising hopes for new treatments affecting disease progression [4].

The provision of time and healthcare resources are currently focused on the treatment of established OA (tertiary prevention), defined by chronic pain and manifest radiographic signs of osteoarthritis. Classification criteria [5] and clinical guidance [6, 7] have been issued for such patients with established and advanced joint damage. However, patients that fulfill these criteria commonly have significant joint damage and resultant altered biomechanics, and often altered pain processing due to the chronic pain. Effective treatment is therefore difficult. We regard this current mode of managing OA as being 'reactive', with treatment modalities added as symptoms worsen and the disease progresses towards an end stage, often, but not invariably, requiring joint replacement. This 'reactive' management mode of a common, costly and severe disease can be compared with the now taken-for-granted 'proactive' emphasis on early diagnosis, management and prevention of other common conditions like diabetes, cardiovascular disease, Alzheimer's disease, rheumatoid arthritis, osteoporosis, and cancer. To change our current reactive approach of managing OA into a proactive one, with an emphasis on secondary prevention, we need to identify risk factors and diagnose OA early, for a greater chance to prevent or slow disease progression.

We propose that treatment will be most effective in early disease. Unfortunately, despite the availability of diagnostic and classification criteria for established OA [8], the lack of a consensus on what represents early knee OA severely limits the feasibility of clinical trials. The Fibroblast Growth Factor 18 trial provides an illustrative example, where patients had severe OA of the medial femoral condyle and milder disease in the lateral compartment. Analysis of secondary outcomes revealed no change in cartilage loss in the medial compartment with severe OA, but a dose-dependent statistically significant reduction of cartilage loss in the lateral compartment, characterized by milder OA [9]. Defining 'early OA' would allow testing of an intervention in a patient population that is more likely to benefit

from the intervention. Identifying OA in its earliest stages in the primary care setting would also allow the optimal multimodal management of the disease with e.g. patient education and exercise [10, 11]. Proactive modification of the course of disease, before destructive processes irreversibly compromise the joint, could prevent development of chronic pain before it elicits sensitization locally and centrally, and before functional impairment leads to deconditioning. Such early intervention could limit indirect costs of the disease caused by loss of work participation, sick leave, lost productivity, premature retirement and lifetime disease burden. In most countries, we would identify and manage these patients in primary care. To achieve this aim, we need to be able to identify early OA by signs and symptoms, joint structure changes, or soluble biomarkers. We also need tools to measure its progression and response to intervention in clinical studies.

However, we lack consensus criteria for classifying early OA. Importantly, classification criteria are standardized definitions primarily intended to create homogeneous patient subsets, recruited from first or second line caregivers, for the purpose of clinical studies [12, 13]. The First International Early Knee Osteoarthritis (IEKO) workshop, held in Tokyo, Japan in November 2014, and hosted by the Japanese Society for Early Osteoarthritis, gathered an international group of about 85 experts and participants (list see below in acknowledgments) to develop a first draft of classification criteria for early knee osteoarthritis. To add to its clinical relevance, a second independent, international group has produced a core set of outcome criteria for early OA (Emery et al, submitted).

Methods

The invited experts were selected based on their internationally recognized area expertise, experience and availability to discuss a first draft of classification criteria for early knee osteoarthritis. Participants were selected to represent the following areas: rheumatology, orthopedic surgery, radiology, physiotherapy, epidemiology, health sciences, experimental research, basic and translational science related to OA. A list of workshop participants is provided in acknowledgements.

It was agreed at the outset of the meeting that the starting point ('base case') for the discussions would be the patient presenting with incident knee symptoms and/or signs in a primary care setting, with no clear history of recent trauma-.

The workshop was divided into sessions around topics relevant for classification of the early OA patient, with short state of the art presentations, followed by breakout sessions where specific questions were discussed in 10 smaller parallel breakout groups of 6-9 participants. A selection of questions was discussed and compiled before the meeting between the scientific coordinators (FL, LSL) and the session chairpersons. Sessions were moderated by facilitators and group discussions by rapporteurs. Discussed topics included: general concepts of early and established OA; symptoms, function and signs; structural assessment by X-ray imaging, MRI, arthroscopy, or ultrasound; molecular markers; and the role of inflammation and biomechanics. Following the breakout discussions, the rapporteurs presented the consensus answers of each group to the questions, followed by a general discussion. The facilitator concluded each session with a résumé of the consensus discussion, approved by the participants.

In a final session, the chairs of the workshop presented an overall summary based on previous session summaries, followed by a general discussion with any summary modifications and final version approved by participant consensus. With FPL and LSL as chairs, rapporteurs and co-rapporteurs merged the session summaries into a first draft.

Results

Symptoms, signs and function

Participants agreed that symptoms and signs may be present at the earliest stages of the disease and therefore have potential for classification of early OA. To be useful criteria, participants further agreed that knee symptoms and signs should precede a diagnosis of established OA, defined as knee symptoms and Kellgren & Lawrence (KL) grade 2 or greater ($KL \geq 2$) radiographic changes [14] [15].

As summarized during the session, several observational studies have explored knee pain and other symptoms and signs [16-21], or symptoms and pre-radiographic joint changes on

magnetic resonance imaging (MRI) [22-25] as predictors of future radiographic knee OA. These studies have shown that pre-radiographic joint changes detectable on MRI may predict incident radiographic knee OA by several years. However, as discussed in the imaging section of this report, MRI shows lesions in the tibiofemoral joint in most middle-aged and older people with no evidence of radiographic OA, regardless of pain [26, 27]. This suggests that much further work will be needed to clarify associations between knee symptoms and MRI features.

Importantly, incident knee pain in the adult, in particular when using stairs, may predict incident radiographic knee OA by 2-3 years [28]. Isolated patellofemoral OA is often present in those with knee pain and predates tibiofemoral OA; signs and symptoms associated with isolated patellofemoral OA are crepitus and difficulty with descending stairs [29]. Joint line tenderness predicts the progression to established osteoarthritis in cohorts of patients with knee pain [30, 31].

In a cohort of early and established knee OA, the early OA group reported pain and symptoms assessed by KOOS domains that were comparable with the established OA group [32]. Loss of function may also be a relevant criterion to mark incident early OA. As an example, in a cohort study comparing healthy controls to patients with early knee OA defined primarily by MRI [33], and patients with established knee OA, the early OA group had significantly worse KOOS pain and ADL score compared to the control group [34]. Of note, isometric and isokinetic quadriceps strengths were lower, and varus thrust increased in the early OA patients, while other functional measures were not different [35].

Finally, a systematic review of prognostic factors for progression of clinical osteoarthritis of the knee found strong evidence for multiple prognostic factors but the large variety in definitions of clinical knee OA and disease progression hindered meta-analyses. Authors noted that evidence for the majority of determinants was limited or conflicting and that only few studies had used pain progression as an outcome [36].

Breakout session

During the round table discussions, four issues relevant to the development of classification criteria for early OA were discussed:

A) Should pain be included in the classification criteria? How would we describe this in terms of duration of pain and intensity?

Consensus was reached that pain should be included in the classification criteria and that ideally duration, severity and/or frequency should be specified. Consensus opinion considered the KOOS score the most appropriate currently available tool , as it includes all the WOMAC 3.0 questions, encompasses multiple domains of function, has minimal (10 %) ceiling effect (higher score indicates less impairment) and no floor effect [37]. This would make it applicable to the traditional older OA patient, but also particularly useful in younger people for whom evaluation for early OA would be relevant. The duration of symptoms was also discussed during the break-out session. The general consensus was that in early stages the pain comes and goes, and that there should have been repeated pain periods; the duration and frequency of these periods were discussed but not further defined based on lack of evidence. Previously, pain on most days of any one month of the last year was proposed [38].

Compartmental involvement, patellofemoral or tibiofemoral, and how this is presenting in early OA, was not discussed at the meeting. Future studies should further explore this parameter in the early OA population.

B) Should we categorize the nature of the pain as e.g. inflammatory vs mechanical, allodynia, peripheral/central pain?

The groups agreed that while insufficient data are available to link the diagnosis of early knee OA to one or more specific pain patterns, the consensus recommendation was that specific concomitant pain syndromes such as fibromyalgia should be excluded from clinical studies in early knee OA.

C) Should other symptoms and signs such as discomfort, locking, crepitus, or instability be included?

There was no overall consensus reached, in that four groups felt that crepitus should be included, three for joint line tenderness, three for stiffness and two for swelling. Discomfort, locking and instability were not thought to be useful in early OA.

D) Should function be included in the classification criteria, and if yes, how should it be defined and measured?

Due to the challenges of performing objective functional tests in primary care, consensus was that subjective function scores were the most appropriate [39], although simple tests

such as walking speed, chair rise and simple muscle strength tests could be useful. With the swift advent of mobile 'wearables' to measure functioning in daily life with ever increasing precision, it may soon be possible to include these types of assessments as part of the classification criteria, although they may be more suited as outcomes.

Consensus statement

Pain and self-reported function should be measured using validated tools such as KOOS. Signs, such as joint line tenderness, effusion and crepitus may also be appropriate for use in the classification criteria of early OA.

X-Rays, Ultrasound, Arthroscopy

Participants agreed that ultrasound and arthroscopy, although used for visualizing joint structures in some settings, were not generally useful in the setting of primary care. The discussion focused on the utility of plain radiographs in the setting of early OA. While radiographic examination may not always be needed to diagnose knee OA in the primary care setting, evidence was presented in the session that even doubtful features of OA, such as minor osteophytes, add considerably to the predictive value of age, gender, BMI and 'questionnaire-based' factors, biomarkers, or a genetic risk score for subsequent OA development [40]. Participants agreed that validation of classification criteria for early OA would be accomplished by demonstrating high positive predictive value of the criteria for subsequent incident symptomatic, radiographic OA.

Breakout session

Should knee radiographs form part of the classification criteria?

The consensus position of the participants was that for several reasons radiographs should be included. Firstly, without a knee radiograph, it would be difficult to rule out established OA, as symptoms and signs of early and established OA may overlap. Secondly, in the clinical setting, a radiograph would help rule out differential diagnoses such as stress fractures and osteonecrosis. The final reason was that there was recent evidence that changes in bone shape can be detected early in the course of knee OA and that in the future, this may provide a useful predictor or criterion for classification [41].

Which type of radiographic examination should be performed and how should it be assessed?

Consensus was reached that two views would need to be taken to address the tibio-femoral (TF) and patella-femoral (PF) joints. To assess the TF joint, a fixed flexion Posterior-Anterior weight-bearing radiograph should be used with a standardized acquisition protocol, including placement of a measurement tool (sphere or ruler) on the film. The skyline view (supine), following a standardized protocol was the preferred view to assess the PF joint. Radiograph assessment would normally be performed according to local clinical policies, however the group did discuss the optimum method for assessing radiographs for research purposes, as this would require research to validate the new criteria. Assessment should be performed using well-validated semi-quantitative atlases. However, there was considerable discussion about the choice of atlas. The limitations of the KL atlas were discussed, particularly the scoring of grade 2 and its variability across different centers and cohorts. In the absence of obvious alternatives with significantly better performance, it was agreed that a KL grade of 0 or 1 should be used in the classification criteria. The scoring of the patellofemoral joint was less certain as it was not scored as part of the original KL criteria; however, several alternatives, such as the OARSI scoring system (with scores reflecting a definite osteophyte and/or joint space narrowing) do exist [42], and would need to be explored.

Consensus statement

There was a unanimous recommendation that radiographs should be used and that a KL grade of 0 or 1 should apply for early OA. Alignment with OARSI recommendations with regard to image acquisition and assessment was advised [43].

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides a highly sensitive, but not necessarily specific method to detect structural joint changes. These changes can be assessed qualitatively, semi-quantitatively, or quantitatively by semi-automated or fully automated methods. MRI can also be used to assess tissue properties using compositional techniques. MRI is resource

consuming, expensive, and usually not available in routine primary care. However, for research and validation of early OA classification criteria, MRI will be an important tool.

All speakers emphasized the sensitivity of MRI to detect joint tissue changes associated with osteoarthritis, but also that structural changes commonly associated with osteoarthritis are very common in the population, irrespective of joint symptoms, and increase in prevalence with age. For example, it has been reported that meniscal tears were present in 15% of women and 30% of men in an unselected population between ages 50 and 59, regardless of knee pain [44]. The prevalence increases with age. Cartilage damage, osteophytes, bone marrow lesions and meniscal tears were very commonly present in knees of persons aged between 50 and 90 years *without* signs of osteoarthritis on routine knee radiography, again regardless of knee pain [27, 45]. Therefore, a major challenge lies in the common occurrence of these changes in the general population, their modest cross-sectional association with joint symptoms, and their insufficiently documented natural history.

A draft MRI-based definition of tibiofemoral OA was suggested to include the presence of both group [A] features, or one group [A] feature and two or more group [B] features [33, 46]:

Group [A] features include (i) definite osteophyte formation, (ii) full thickness cartilage loss; Group [B] features include (i) subchondral bone marrow lesion or cyst not associated with meniscal or ligamentous attachments, (ii) meniscal subluxation, maceration or degenerative horizontal tear, (iii) partial thickness cartilage loss where full thickness loss is not present, (iv) bone attrition [47].

This tentative definition will need validation in independent study populations. Relevant to this challenge, a recent study presented evidence to suggest that MRI-detected knee joint lesions in a population at-risk for osteoarthritis (but without plain radiographic signs of OA) are not incidental and may represent early disease in persons at increased risk of definite knee OA [22]. In support, a ‘hidden osteophyte’, undetectable on plain X-ray but detectable on MRI, was predictive of development of knee osteoarthritis within 48 months [48]. Finally, synovitis in OA detected by MRI is associated with knee pain and can precede, by at least a year, incident radiographic OA [49].

Consensus statement

There was general agreement that MRI is a powerful technique that is needed in research on early OA. However, at present MRI is not recommended as an aid to identify or define early OA in routine clinical practice or primary care, in light of lack of validated consensus criteria and the high population prevalence of structural joint changes detected by this method.

Biomarkers

The OA disease process represents a continuum from the earliest changes in cells through molecular changes in the surrounding matrix, having functional and structural consequences on the nano and micro scale, to emerging symptoms and structural changes detectable by imaging, and to the eventual joint destruction in some individuals. As our techniques to detect changes earlier in the disease process become more sensitive, we may be able detect OA earlier in the process.

Biomarkers of early OA have been identified in the context of minimal cartilage damage. Examples include sphingolipids, serum IL-6, CD14, CD163, MCP-1, MIP-1 beta, interferon gamma and COMP and is being further expanded by unbiased proteomics studies [50-54]. Biomarkers of early OA were also identified in a preradiographic OA context that may predict the progression to radiographic disease. These include serum COMP, hyaluronan, MMP-3 and -17, osteocalcin, IL-15, plasminogen activator inhibitor-1 and soluble vascular adhesion protein-1 [55-59]. Proteoglycan fragments, collagen fragments and metalloproteinases are also detectable after injuries that predispose to OA such as anterior cruciate ligament (ACL) and meniscal injuries [60-65]. Persistence of such biomarkers later after injury may identify patients at higher risk of OA [66].

The combination of several biomarkers reflecting different pathological processes may better classify early OA than a single biomarker. Support for this concept was provided by a study of multiple biomarkers (urine CII neoepitope, serum hyaluronic acid, and serum pyridinoline); their integration led to higher sensitivity, specificity and predictive ability to distinguish early OA patients from age matched controls [67]. Complex statistical modeling is

required to integrate biomarkers, imaging and clinical data to predict well-defined outcomes.

Breakout session

What should biomarkers measure? Rate of cartilage loss? Residual cartilage? Catabolism/anabolism? Inflammation? Underlying bone? Meniscal damage? Mechanistic events such as disrupted/activated pathways?

The group considered that these parameters may each have importance in different contexts. Measuring the rate of cartilage loss or other tissue parameters using biomarkers would be desirable, but challenging due to the apparent fluctuation of these parameters in individual patients over time, particularly in early OA. Biomarkers reflecting cartilage anabolism and catabolism, bone turnover, and pathogenic pathways for patient stratification by disease mechanism and activity were considered very attractive since they may aid in identifying the right therapeutic target. However, there was full consensus that these aims have not yet been fulfilled and were relevant primarily for research, and that no single marker or set of OA biomarkers have currently any utility in clinical routine.

Consensus statement

Although biomarkers may have future utility in early OA classification and prediction of progression, no individual or set of biomarkers is yet robust enough.

Final Session

After the open discussion sessions, a group including the chairpersons, rapporteurs and co-rapporteurs, met to refine a draft proposal.

There was, within this group, consensus that three classes of criteria should be used (Table 1):

1. *Patient based questionnaires* - preferably Knee Injury and Osteoarthritis Score (KOOS) that includes subdomains of pain (9 items), stiffness and other symptoms (7 items), function and daily living (short PS version 7 items), and knee related quality of life (4 items). The KOOS was chosen as it contains the full set of WOMAC questions, and has

additional domains making it more relevant to early OA. The use of KOOS thus allows comparison with results from extant older cohorts, and calculation of a WOMAC score. The choice of questionnaires may be further adapted as more data, also from other cohorts, become available.

2. A second set of criteria is based on *clinical examination*, with two preferred clinical examination findings being joint line tenderness and crepitus. Crepitus was included as it was decided to also include patellofemoral OA and not only tibiofemoral OA. Other clinical signs such as palpable warmth, effusion (refill test), bone tenderness and reduced range of motion were not considered signs of early OA so were not included.
3. *Standardized weight-bearing X-ray examination*. We agreed on the radiological criteria being KL 0 or 1, with KL ≥ 2 classified as definite OA. Two views are recommended, weight-bearing posterior-anterior fixed flexion of both knees, and a bilateral skyline (supine) view. Alignment with the OARSI recommendations was proposed [43].

It was agreed that these draft criteria need to be refined and validated in several different population-based cohorts to explore what proportion of patients defined with early OA did indeed progress to develop definite symptomatic, radiographic OA as defined by the ACR criteria .

Discussion

These draft recommendations result from consensus discussions at the first international early knee osteoarthritis workshop in Tokyo, Japan, and are intended for the international community to modify and validate.

OA remains a chronic complex disorder with modestly effective symptom relieving treatments, no approved disease modifying treatments, and with joint replacement surgery offering the most substantial relief of symptoms for severe, advanced disease. Current approaches to advance the field include stratifying patient populations into different phenotypes in order to target treatments more effectively. However, there is a growing belief that the lack of disease modifying treatments is also due to the complexity of more

advanced OA disease that involves the whole joint, with degrees of irreversible damage, pain sensitization and muscle deconditioning. It is unlikely that in an advanced disease stage targeting one pathway or one tissue will affect the disease process sufficiently in its course to be clinically relevant. It is therefore critically important to identify early OA, before these factors are all in play. This would allow us to target individuals with secondary prevention and treatment strategies more effectively with the possibility of preventing irreversible damage. We are in essence looking for the opportunity to diagnose and treat the equivalent of angina in the field of coronary artery disease to prevent myocardial infarction.

We propose that the development and validation of classification criteria for early OA would impact the field and create a positive momentum for a disease that is perceived as being both highly challenging and unlikely to be resolved by one single “wonder drug”. There is a strong belief that many treatments, pharmacological and non-pharmacological, would be more effective in early OA, by targeting single tissues or pathways before the disease becomes more complex. Importantly, classification criteria such as those proposed here do not equal diagnostic criteria, but are intended for research, to investigate new treatment strategies of early phases of the disease process and to define valid outcomes.

We are aware that this is just the beginning of a process of producing consensus classification criteria, and that validation and further iterations of these criteria will be required. The workshop participants agreed that part of the validation process could use existing population based cohorts for testing several constructs, as each will have its own limitations and strengths:

1. What is the specificity and sensitivity of the proposed criteria?
2. Do these criteria associate with MRI features of early knee OA?
3. Do they predict, over at least 5 years
 - a. the onset of ACR defined OA?
 - b. the onset of radiographic knee OA?
 - c. the need for total knee replacement?

Several community based cohorts are available, such as the CHECK study in the Netherlands, the CAS-K(nee) population in the UK, the Osteoarthritis Initiative in the US (<https://oai.epi-ucsf.org>), the Chingford, Framingham, JoCo, and ROAD cohorts, that could serve to refine and validate these criteria[68], [69-73]. MRI-related imaging and biochemical biomarkers

could enter the classification criteria of early OA as they prove their utility and become more readily accessible. However, they will need high-level computational analysis to integrate them with the current criteria in models to assess both their incremental predictive ability and cost effectiveness.

We are now seeking to define and treat OA at an earlier stage, a stage that today may not be generally recognized as being 'real OA', so that we may intervene when there is better hope for secondary prevention by slowing or stopping further development of symptoms and tissue destruction. While doing so, we must be cognizant of the pitfalls of 'overdiagnosis' and 'overtreatment' [74, 75]. The proposed classification criteria for early OA of the knee represent a starting point to facilitate their refinement and validation for research and to investigate new treatment strategies of early phases of the disease. The participants of the workshop were all in agreement that this is an opportunity for the field to advance the understanding and treatment of OA. Similar efforts should also follow for other joints commonly affected by OA such as the hip and hand.

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Statements of potential conflict of interest

No potential conflicts of interest have been reported.

Role of authors

All the authors reviewed and approved the final version of the manuscript. FL, NA and LSL wrote the first draft, coordinated the writing of the paper and brought it into its final form. As Chairmen of sessions, Sita Bierma- Zeinstra, F Dell'Accio, V. Kraus, N. Arden and LS. Lohmander wrote the resumé of their respective sessions. KN and IS were the local organizers of the workshop and critically reviewed the paper for its content.

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Table 1

Draft Proposal for Classification Criteria for Early OA of the Knee

A. Patient based questionnaires: Knee Injury & Osteoarthritis Outcome score: 2 out of the 4 KOOS subscales need to score “positive” ($\leq 85\%$)

1. Pain (9 items, including information on pain intensity, frequency and duration)
2. Symptoms, stiffness (7 items)
3. Function, daily living (short version: 7 items)
4. Knee related quality of life (QOL, 4 items)

B. Clinical examination: at least 1 criterion needs to be present

- Joint line tenderness
- Crepitus

C. X-rays: KL grade 0-I standing, weight bearing (at least 2 projections: PA fixed flexion and skyline for patellofemoral OA)