Establishing outcome measures in early knee osteoarthritis

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Abstract

The classification and monitoring of individuals with early knee osteoarthritis (OA) is an important strategy for the design and evaluation of therapeutic interventions. Such an approach requires the identification of appropriate outcomes measures. Potential outcome measures for early OA include patient-reported outcomes (such as measures of pain, function or quality of life), features of clinical examination (such as joint line tenderness and crepitus (that is, grating and crackling sounds), objective measures of physical function, levels of physical activity, movement biomechanics, structural assessments such as magnetic resonance imaging (MRI) and biochemical markers in body fluid. Patient characteristics such as adiposity and biomechanics of the knee could also have relevance to early OA. Importantly, future research is needed to enable the selection of outcome measures that are feasible, reliable, and validated in those at risk of OA and an early knee OA population. In this Perspectives paper, potential outcome measures of individuals with early symptomatic knee osteoarthritis (OA) are discussed, including those that could be of use in clinical practice as well as research settings.

[H1] Introduction

Osteoarthritis (OA) is a leading cause of chronic pain, disability, and health care utilization, with knee OA contributing the greatest burden[1-4]. OA is associated with increased rates of comorbidity (for example, obesity and heart disease)[1] and ranks the 13th [2] most burdensome amongst all forms of disability world-wide. The incidence, burden and socioeconomic impact of OA is considerable and growing[3, 5]. Therefore, a shift in the treatment approach is needed from treating patients once they have established OA to a proactive approach that focuses on mitigating risk factors. The classification and monitoring of early OA, on a trajectory from normal to symptomatic and/or radiographic OA, would provide an opportunity in clinical practice and research for the development and evaluation of interventions to prevent or slow down the disease process at a time it is probably more amenable to modification.

Although the definition of early OA and appropriate outcomes are under development, OA is probably heterogeneous in terms of its presentation and progression. Knee OA might progress slowly over a period of ten or more years, rapidly, or not at all[6]. Predicting the development and progression of disease through identifying risk factors and mechanisms of OA is important in chronic disease management to inform targeted OA prevention and treatment strategies. This strategy is difficult because of the heterogeneous presentation of OA; however, the availability of increasingly sophisticated statistical and computational methods, microsimulation modelling, and large population-based cohort studies make this approach increasingly viable. For example, widely-used online prediction tools are now available for evaluating future risk of osteoporotic fractures and for guiding clinicians in preventive management of osteoporosis[7-9]. Comparable reliable and validated outcomes for early knee OA will inform the evaluation of risk factors for the progression of early OA. More than one set of risk factors and models will probably be needed to predict early OA in the future. The Rotterdam and Chingford studies (two prospective population-based studies) have demonstrated an ability to predict incident radiographic knee OA using a combination of clinical, genetic, and radiographic factors[10]. When performing risk assessment and creating a predictive model for early knee OA, many aspects need to be considered: the definitions of the outcome and prognostic factors; the duration of the clinically relevant prediction period; and the setting in which the risk prediction tool will be used (for example, primary care, secondary care or a research setting). For instance, expensive and intensive predictive tools such as MRI scans and biochemical markers might be restricted to secondary care and/or a research setting.

In this Perspectives article, we highlight considerations for best practice in the selection of outcome measures for use in clinical and research settings to evaluate patients at initial presentation of early knee OA across different outcome domains: patient-reported outcomes, clinical examination, physical function, adiposity, physical activity, nutrition, biomechanical outcomes, imaging features and biochemical markers[11]. We suggest outcome measures that could be considered for use in individuals with early knee OA in clinical care and research settings using published evidence (primarily from post-traumatic and

established OA populations), emerging evidence (ongoing studies), and clinical expertise (Box 1). The outcome measures highlighted are relevant to individuals that are at risk of OA and fit the provisional criteria for early knee OA based on patient reported outcomes of pain and function, together with clinical signs (joint line tenderness or crepitus) and a radiographic Kellgren-Lawrence (KL) grade of 0-1 [12]. Although proposed as important evidence-informed clinical outcome measures, these outcome measures will require additional validation and possible modification to suit local primary care and other healthcare settings, as well as periodical updates.

[H1] **Patient-reported outcomes**

Patient-reported outcomes are any report of a patient's health status that comes directly from the patient without interpretation by others (for example, the clinician). These measures commonly take the form of a questionnaire. Most relevant patient-reported outcome measures have been developed to either assess individuals with a knee injury (for example, International Knee Documentation Committee 2000 (IKDC2000)) or established OA (for example, Western Ontario and McMaster Osteoarthritis Index (WOMAC)); although, one questionnaire has been developed to cover the full spectrum from injury to established OA (the Knee Injury and Osteoarthritis Outcome Score (KOOS)). The relative merits of these and other available instruments that measure self-reported pain, function, and quality of life have been the subject of previous reviews[13, 14]. Today measures, such as PROMIS, are often developed using computer adaptive strategies which may also prove to be relevant for use in people with early knee OA[15]. Many of the considerations that influence the choice of measure in established OA (for example, respondent burden, cost or availability) apply also in early OA.

Ultra-brief (one or two domains) unidimensional generic measures, such as the 11-point Numerical Rating Scale (NRS-11), the 36-Item short form health survey (SF-36) bodily pain scale (SF-BP 36), have been recommended in previous reviews for established OA[16] and are probably applicable also in early OA.

However, the disadvantage of unidimensional measures is a restricted view of the pain character and intensity[16, 17], which is probably inappropriate based on emerging evidence from qualitative studies in patients with early knee OA[18-20]. For instance, these patients report that their initial symptoms can be experienced as 'an awareness' of the knee, loss of confidence, or needing to 'be careful' as opposed to 'pain'. The KOOS knee-related quality of life subscale includes consideration of questions on these aspects[14,15]. Further, reporting OA pain as 'constant' or 'present on most days' might give floor effects (i.e., most individuals may report at the lower end of the scale) in early OA as these patients often report episodic and intermittent pain with certain activities. For example, pain during ascending or descending stairs seemed to be the earliest functional difficulty reported in the OA initiative[21]. Accordingly, the intermittent and constant assessment of pain score (ICOAP) questionnaire, which includes a subscale on intermittent symptoms, has an increasing amount of evidence supporting its' reliability and validity[22].

Another important consideration is that the early phase of knee OA is often associated with the emergence of adaptive behaviour. Symptom frequency and intensity might be minimized through the selection of behaviours (for example, performing some activities less often), optimization of behaviours (for example, advanced planning of activities, including anticipatory analgesic use), and compensatory adaptations (for example, modifying the way activities are performed)[23]. Therefore, consideration of adaptive behaviour is a legitimate topic for outcome measurement in early OA[24], an example of which is the Questionnaire to Identify Knee Symptoms (QuIKS). QuIKS includes questions such as "I am considering stopping a favorite activity due to my knees" and "I am considering changing my exercise routine due to my knee problems"[25].

The KOOS was developed for self-reporting of patient-relevant outcomes across the lifespan, from time of knee injury and potential knee OA onset to severe OA[26-29]. In five separate subscales this tool assesses perceived pain and other symptoms (e.g., stiffness, grinding, catching), perceived difficulty with function during daily life and sport and recreational activities, and knee-related quality of life. The KOOS measurement properties have been reported in studies of young, middle-aged, and elderly groups with

knee injury or OA, and across the spectrum of[14]. A comprehensive literature search identified 37 eligible papers evaluating KOOS measurement properties in participants with knee injuries and/or osteoarthritis (OA) and found that KOOS demonstrates adequate content validity, internal consistency, test-retest reliability, construct validity and responsiveness for age- and condition-relevant subscales[14].The KOOS is feasible to administer electronically and in paper form and KOOS scoring instructions and population-based KOOS reference data are available. In addition, longitudinal KOOS data have been collected from more than 100,000 patients in surgical registries of anterior cruciate ligament reconstruction and knee replacement facilitating comparisons to many different populations[30, 31]. In addition, for the interested researcher, KOOS data are freely available and collected from the cohort of patients who are at increased risk of OA and the cohort of patients with established disease from the NIH-sponsored OA Initiative[32]. The OA initiative also collects a wide range of other self-reported, clinical and imaging data[32]. The cohort at risk include people with symptoms and two or more risk factors (including knee injury) but without radiographic OA[32].

The ICOAP was designed to evaluate the pain experience in people with OA. It includes pain intensity, frequency, and impact on mood, sleep and quality of life. It is intended to be used alongside a measure of physical function[22]. OA-specific measures developed for more advanced OA cannot be assumed to have adequate psychometric properties when applied to early OA. Yet, the requirement for adequate performance in early OA must be balanced against the benefits for a coherent evidence base that comes from using common measures across the spectrum from early to advanced OA. Of existing measures, the KOOS and ICOAP seem to best strike this balance and are therefore strong candidates for evaluating early knee OA (Box 1), particularly as these instruments focus on different aspects; both have the advantage of being freely available. Published reviews of the psychometric properties of these two measures require systematic updating with specific attention to their performance in early OA.

[H1] Clinical examination outcomes

Clinical examination outcomes are relevant in research and are easy to perform in primary care. Joint line tenderness (tibiofemoral and/or patellofemoral joint lines) at baseline was suggested to be a strong predictor of five-year pain progression (moderate progression adjusted OR=3.9 (95% CI; 2.3 - 6.6)[33] in the CHECK cohort (n=705) that included patients with newly onset knee pain or stiffness[34]. Several studies have evaluated the ability of physical signs to predict the clinical onset of structural radiographic OA in patients with an increased risk of OA[33-37]. Data from the HONEUR Study, which included 549 participants who were recruited at the first presentation of knee pain in primary care, suggested that joint line tenderness, crepitus (that is, grating, crackling, popping sounds), pain with passive flexion, and a self-reported swollen knee predicted incident radiographic tibiofemoral knee OA after 6 years[35]. Using MRI features of knee OA as an outcome measure, data from the general population Rotterdam Study showed that joint line tenderness together with the 'feeling of giving way' were associated with the incidence of tibiofemoral knee OA, whereas crepitus was identified as a good predictor of patellofemoral OA[36, 37].

Easily assessable measures from physical examination might be associated with future OA development, including joint line tenderness and crepitus, even in the absence of radiologic findings of OA (Box 1). Clinical examination of these features had good inter-observer reliability in a population with evident knee osteoarthritis if a standardised approach to such assessment is used[38]. However, these clinical assessment components require further examination of reliability and validation for research settings in early knee OA and standardization for use in clinical settings.

[H1] Physical function outcomes

Given that the early pre-radiographic stage of OA is associated with intermittent symptoms and adaptive physical behaviour, the clinical evaluation of patients with, or at risk of, early knee OA should incorporate robust outcome measures of physical function[39]. Currently, no consensus exists regarding which outcomes are most relevant for use in this population. For the purposes of this Perspective article, physical function is operationally defined as 'physiological functions' or 'the ability to move around and to perform daily

activities' that can be classified as 'body functions and structure' or 'activities and participation', respectively, using the World Health Organization International Classification of Functioning, Disability and Health (ICF) model[40]. As physical function is multi-dimensional, both performance-based and physical impairment measures (which might require specialized pieces of equipment and raters) are discussed in this section. Emerging evidence suggest that some of these outcome measures might be suitable for the evaluation of early OA and those at risk of OA (Table 1)[41-46].

A range of performance-based measures are available although the degree to which their measurement properties are established and the range of populations they have been used in varies (Table 1). Measures that have undergone fairly extensive investigation include the Single Leg Hop for distance test[43, 44, 47-50], the Cross Hop for distance[43, 47-51], the 6-meter Timed Hop Test[43, 47-50], the Star Excursion and similar Y-balance Btest[44, 51-56], the 30-second Chair Sit-to-Stand Test[57-59], and the 6-minute walk test[41, 42], while there is emerging evidence for the Vertical Drop Jump [44, 60], the Single Leg Squat [44, 61-63], Unipedal Dynamic Balance test [44, 64] and 20-meter Shuttle Run[44, 65]. The most commonly reported outcome of physical impairment is quadriceps muscle strength[44, 47, 48, 52, 66], however, there may also be value in considering the strength of other lower extremity muscles including the hamstring, hip abductor and hip adductor muscles[67]; although, insufficient information is available to advocate for specific contraction mode (i.e., isotonic, isokinetic or isometric) or type (i.e., concentric or eccentric).

Because of floor and ceiling effects (i.e., most individuals report a minimum – floor, or maximum – ceiling score), separate measures are required to cover the wide range of ages and abilities of patients with early knee OA in both clinical and research settings . Functional outcomes that should be considered for use in research and in clinical physical and exercise therapy practice based on their measurement properties and ability to span the full spectrum of patient age and abilities include the Single Leg Hop for distance, 30-second Chair Sit-to-Stand Test, 6-minute walk test, Star Excursion Balance Test and a quadriceps strength measure. The performance-based outcomes should be administered in a standardized, validated and

reproducible fashion to enable detection of change over time; video demonstrations and explicit instructions for standardized testing are available online (see related links). Further research validating functional outcomes in 'at risk' (e.g., intra-articular knee injury, obesity, varus/valgus alignment abnormality) and 'early-OA' populations is required and this research should inform the periodic updating of these suggested functional outcomes.

[H1] Modifiable lifestyle-related outcomes

The presence of modifiable risk factors related to lifestyle, such as obesity, dietary inadequacies, and physical inactivity might lead to accelerated disease onset and progression through a combination of mechanical and systemic mechanisms[68]. Identifying these modifiable risk factors in early knee OA is important for the prevention of OA.

Several measures of adiposity or weight have been studied in established OA, but less so in early OA. These include BMI, waist-height ratio (WHR) and waist circumference[69-73]. The location of fat deposits influences their metabolic and inflammatory potential and therefore may be important considerations[74] . A high waist-height ratio or waist circumference (indicative of abdominal adiposity) was associated with an increased risk of OA progression[73]; however, neither outcome was associated with the loss of tibial or patellar cartilage volume or defects in adults in the community with pre-radiographic OA [75, 76]. To better understand this relationship, a distinction between subcutaneous and visceral adiposity using valid assessment techniques (e.g. MRI or CT assessment) is likely needed. Measurements of fat mass (kg), percentage fat mass (percentage of total mass) and fat mass index (FMI; fat mass/height^2), can be obtained using dual-energy x-ray absorptiometry or bioelectrical impedance analysis, hence permitting a direct measure of total adiposity[77]. Total fat mass is positively associated with an increased risk of knee cartilage defects and the presence of bone marrow lesions in healthy individuals (aged 25-60 years)[78] and medial tibiofemoral cartilage volume loss over 2-10 years in adults aged 51-81 years[79, 80]. A systematic review

reported moderate evidence for the relationship between obesity (that is, increasing weight, BMI or total body fat mass) and the presence of bone marrow lesions in the knee in individuals with OA[72]. In addition to contributing to an increased mechanical load, adiposity is thought to have a metabolic and pro-inflammatory function in OA; therefore, a direct measure of adiposity such as fat mass, percentage fat mass or FMI might be useful in the assessment of early-stage OA[81-84].

Physical activity is a modifiable outcome that might delay the onset of functional limitation, prevent obesity, and is essential for normal joint health[85]. In addition, physical activity can reduce pain and disability among individuals with OA and increase their physical performance and self-efficacy[86-88]. Light or moderate intensity physical activity might protect against the onset of disability related to symptomatic OA, whereas a sedentary lifestyle or high levels of strenuous physical activity are considered risk factors[89-91]. Many variations of self-reported measures of physical activity exist including global or short recall questionnaires, although most have limited accuracy[89-91]. Wearable monitors that measure body motion can be used to assess physical activity and energy expenditure. The most commonly used sensor, validated across multiple populations, is an accelerometer (for example, Actigraph)[92], which captures frequency, intensity, and duration of physical activity in a time-stamped manner. The large selection of off-the-shelf accelerometers, often contained in mobile phones, might be more suitable in a primary care setting to measure physical activity as they are less expensive, easier to use, and widely available[93, 94]. Most accelerometers, however, are not validated to measure cycling or swimming. In general, objective measures of physical activity such as accelerometer outcomes compared with self-reporting have stronger relationships with function in OA[95] and are a more accurate assessment of physical activity and sedentary lifestyle.

Nutrition interventions such as weight loss[96, 97] are lifestyle-related changes that can potentially improve OA symptoms. Beyond the link between obesity and knee OA (and therefore the important contribution of weight loss)[98, 99], the contribution of nutritional factors is an emerging and important area of research,

279 although limited clinical evidence is available to date. For example, low dietary intakes of fibre[100] or omega-
280 3 polyunsaturated fatty acids[101], and high fat diets[102] are risk factors for OA and/or worsening of pain in
281 OA and might therefore warrant monitoring in early OA. Many of the nutrients or dietary patterns tested
282 to date probably contribute to pathology via alterations in body weight or inflammation, although the
283 direct effects of these factors requires further investigation. The tools to monitor dietary intake are
284 numerous (for example, the Food Frequency Questionnaire (FFQ), 24-hour dietary recall (either the paper-
285 based or web-based automated self-administered 24-hour dietary recall (ASA24) assessment tools[103]) and
286 the 3-day or 7-day weighed food record) and need to be assessed for each clinical or research setting. In
287 addition, tools to assess adherence to diets that reduce inflammation such as the Mediterranean Diet
288 Adherence Screener[104] might also warrant use in future.

289 Hence, objective measures of adiposity are desirable. BMI is a useful outcome measure for assessing
290 adiposity in a primary clinical setting because of its familiarity, validity, and reference ranges. However,
291 BMI has limitations for use in young athletes. Although weight loss can improve OA symptoms, further
292 research is needed to identify a means of assessing important OA-related nutritional factors. Assessment
293 of physical activity using a validated accelerometer, to accurately capture activity through each domain
294 and intensity, is a promising area that requires future study.

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296 **[H1] Biomechanical outcomes**

297 Biomechanical outcomes are measures of joint mechanics typically collected in a research setting, but
298 sometimes taken in a primary care setting. Joint mechanics can be employed to assess OA severity, but
299 also for understanding the causes of OA onset and progression. For example, altered joint mechanics
300 following knee injury might contribute to the onset and development of post-traumatic OA[39]. Indirect
301 evidence to support this concept comes from observations of altered joint movement, loading, and muscle
302 activation patterns following injury[105-110], with radiographic knee OA (KL≥2)[111-113], with aging[114, 115] and pre

and post joint arthroplasty[116-118]. Abnormal joint alignment[119, 120], alteration of the external knee adduction moment (KAM) and increased varus alignment are often regarded as indicators of altered joint mechanics associated with increased OA severity[113]. However, joint mechanics in OA might also change because of other factors including loss of dynamic joint stability[121, 122], muscle atrophy[123], neuromuscular inhibition[124], muscle weakness,[125-127] and compensatory muscle activation mechanisms[111, 112, 117]. These changes might alter cartilage loading and contact mechanics. Indeed, some studies indicate that changes in tibiofemoral cartilage contact locations[39, 128], elongated path lengths[129], force magnitudes[106, 130, 131], and deformations[128, 129] are associated with OA onset and progression. In turn, OA progression might be caused by progressive degradation of cartilage through interactions of articular movement and cartilage loading abnormalities, chronic inflammation, resultant tissue remodelling, and other OA risk factors by increasing the susceptibility of cartilage and subchondral bone to damage and degradation at regions inadequately adapted to these altered loads[128, 132-136]. Over time, this process might result in altered cartilage thicknesses and clinically relevant cartilage thinning in different regions of the articular cartilage surfaces . To verify this mechanism, longitudinal data are needed of the joint mechanics, cartilage thickness, and cartilage structure and integrity in OA[137, 138]. Integration of this information with other risk factors for OA-related changes might inform the development of novel patient-specific, diagnostic or predictive models to aid in early patient screening, intervention efficacy monitoring, and the development of new therapeutics[130, 131, 133, 139, 140]. Armed with these data and models, new wearable monitors might enable biomechanical outcomes assessment in the clinic and community[134-136, 141, 142], and might provide the possibility of developing and monitoring personalized treatment plans.

Presently, the joint range of motion is a suggested measure that could be collected in a primary care setting to assess OA severity. The other biomechanical outcomes mentioned above (e.g., KAM, kinematics, electromyography, cartilage loading) although used to understand the mechanisms of OA progression and currently not feasibly collected in most clinical settings, are an important component for consideration in

research settings to inform orthotics design, exercise interventions, bracing, and surgical interventions. In the future, validated wearable monitors might help assess biomechanical outcomes of early interventions in the clinic and community. Evidence suggest that outcome measures are not independent but rather variation in one outcome measure (for example, biomechanical outcomes) can influence the quantitative state of another measure (for example, biochemical markers or imaging outcomes)[143-147]. Thus, future research should consider the interaction between different outcome measures to potentially increase the sensitivity of detecting early OA[132, 144].

[H1] Imaging outcomes

OA is a complex syndrome that at the local level, is best characterised as a whole joint disease involving multiple tissue pathologies. In attempting to characterise and monitor the variety of OA structural components a number of different imaging modalities have been used-the most common amongst these being radiography, ultrasound and MRI. This section will predominantly focus on plain radiography and MRI, as ultrasound has a number of limitations that have constrained its development and validity in this area including observer dependency its' inability to assess bone marrow lesions and to adequately image deep articular joint structures including meniscus and cartilage[148].

MRI plays a major role in the OA research setting, with compositional MRI techniques becoming increasingly more important due to their capacity to assess 'premorphologic' biochemical compositional changes of articular and periarticular tissues. Although radiography remains the primary imaging modality in OA clinical trials and in daily medical practice, known limitations for visualisation of OA features significantly limits the utility of radiography both clinically and in the research arena. Ultrasound can be a useful adjunct to radiography and MRI particularly for the evaluation of synovitis. Emerging hybrid imaging techniques including PET/MRI and PET/CT allow evaluation of the joint with simultaneous assessment of morphological changes and metabolic activities, showing a potential for these hybrid systems to play an increasing role in OA research and clinical practice[149].

Radiographic features of OA are generally classified by the Kellgren and Lawrence (KL) grading system[150] and include joint space narrowing, osteophyte formation, sclerosis, and deformity of bony contours[151]. Minimum radiographic joint space width (JSW) is the gold standard recommended by the FDA for detecting structural changes in patients with knee OA in clinical trials. However, standardized measures of radiographic positioning and fixed location JSW width failed to reach the same degree of responsiveness in knee OA as quantitative measures of cartilage thickness on MRI[152]. Indeed, fixed-location radiographic measures appear not capable of determining the spatial distribution of femorotibial cartilage loss [152]. Moreover, radiographic features such as loss of joint space, sclerosis, and deformity of bone are associated with late-stage OA and are preceded and detected with greater sensitivity by MRI[**153**].

Conventional MRI enables the evaluation of morphological changes related to early OA, including but not limited to cartilage damage, meniscal damage, synovitis, presence of BMLs, and ligamentous damage. In one study of patients with knee pain (n=255, age 40-79 years), BMLs were present in 11% of individuals without radiographic OA (KL = 0), 38% of individuals with pre-radiographic OA (KL = 1) and 71% of individuals with radiographic OA (KL >2)[153, 154]. Similarly, 42% of patients with a diagnosis of symptomatic OA without radiographic features (KL < 2) had BMLs and 57% had cartilage loss[155]. Although a paucity of data exists regarding the timeline of structural changes in the period between a joint injury sustained in youth and the onset of clinical post-traumatic OA, advanced MRI techniques have been used to detect subtle cartilage damage at the time of ACL injury[156]. Furthermore, macroscopic cartilaginous changes, the presence of BMLs, and bone morphology changes might be detectable by conventional MRI techniques as early as two years post ACL reconstruction or other intra-articular knee injury (and potentially before the development of radiographic OA[6, 157-160].

In 2011, a definition of MRI-defined OA was proposed to facilitate earlier detection of OA (Box 2)[161, 162]. In one study of patients who had undergone anterior cruciate ligament (ACL) reconstruction, 19% and 17% of the participants met the MRI criteria for tibiofemoral and patellofemoral OA, respectively, at 1 year[163].

Using the same criteria for MRI-defined OA in patients who participated in a clinical trial of ACL reconstruction, 31% had tibiofemoral OA and 9% patellofemoral OA, respectively, at 5 years[164]. Importantly, some of the changes included in this criteria are undetectable by radiography (i.e. cartilage thickness, bone marrow lesions). Different methodologies can be used to measure structural changes in the knee by MRI including the use of semi-quantitative measures (such as the MRI Osteoarthritis Knee Score (MOAKS)), quantitative measures (including cartilage thickness, bone marrow lesion volume, effusion-synovitis volume and meniscal extrusion) and measures obtained using compositional imaging modalities of cartilage (including T2 mapping, T1ρ mapping, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), sodium MRI and glycosaminoglycan chemical exchange saturation transfer (gagCEST)) which measure cartilage composition and quality[165]. Semiquantitative MRI evaluation can be performed using several available scoring systems such as the MRI Osteoarthritis Knee Score (MOAKS) and the Anterior Cruciate Ligament Osteoarthritis Score (ACLOAS)[154, 166]. For synovitis assessment, contrast-enhanced MRI should be used and semi-quantitative scoring systems based on contrast-enhanced MRI are available to enable clear delineation of the synovium from effusion[167]. In population-based studies, a high proportion of radiographically normal knees have osteophytes and cartilage damage detectable by MRI illustrating the greater sensitivity of MRI as compared to radiography[153]. However, it also highlights the challenge of what is to be regarded as OA and what is part of a normally ageing joint[**168**]. The link between anatomical evidence of OA and patients' symptoms and function is still rather weak[169, 170]. Ultimately, the presence of these findings on MRI require validation by longitudinal follow-up studies to identify their association with subsequent illness related to OA (alteration of patient function and symptoms)[171] to avoid over-diagnosis because of incidental MRI findings[153, 154, 172-174]. Notably, the distinction between pathology and normal features of the ageing joint is unclear and further research to elucidate the clinical relevance of MRI findings in early knee OA is warranted.

Hence, the utility of plain radiography in early OA is limited as only relatively late OA changes are detectable. As technology improves, assessing changes in bone shape or trabecular bone texture of sub-chondral bone might be of use. MRI has superior sensitivity to change and validity in the context of early OA[153]. Although not appropriate for all primary care settings because of the high cost and risk of over-diagnosis, MRI is a critical component of ongoing outcome validation research in early knee OA.

[H1] Biochemical marker outcomes

Biochemical markers of joint tissue turnover can reflect disease-relevant biological activity that might precede structural changes detectable on plain radiographs or even by MRI. Markers detected in blood, urine or synovial fluid may be associated with or predictive of incident radiographic OA. Some biochemical markers detectable in blood, urine or synovial fluid are associated with or predictive of incident radiographic OA. Ideally, biochemical markers of early OA must clearly differentiate between normal (physiological) and pathological tissue turnover as well as between the early stages of the disease and more advanced joint destruction. Biochemical markers must also be unaffected by other disorders and be easily and consistently measurable in a clinical setting[175]. Biochemical markers of early OA might therefore be used to identify pre-radiographic changes at the molecular level, facilitate OA drug discovery, and potentially enable a more rational and personalized approach to healthcare related OA management by prompting earlier and more targeted treatments and interventions [176].

Studies of incident OA have identified some of the earliest molecular abnormalities associated with OA and therefore provide biochemical marker candidates for early OA identification. Serum protein signatures using antibody-based protein microarrays have been shown to detect early radiographic hand or knee OA. Four serum proteins (matrix metalloproteinase-7, IL-15, plasminogen activator inhibitor-1 and soluble vascular adhesion protein-1) were found to be altered in a cohort of patients with OA compared to healthy individuals[177]. Similarly, serum COMP (sCOMP) and hyaluronan concentrations

could predict[178] incident knee joint space narrowing and osteophyte (sCOMP) formation 7 years later in another patient cohort. In another study, incident radiographic knee OA (based on KL scores) over ten years was predicted by high serum COMP concentration (based on KL scores) but low serum aggrecan concentration at the beginning of the study[179]. Notably, though, molecular and structural biomarkers of inflammation at two years after an acute ACL injury did not predict structural knee osteoarthritis at five years[164]. Mean baseline serum osteocalcin concentrations are associated with 3-year incident radiographic hand OA (KL >2) but not knee OA in pre-menopausal and peri-menopausal women[180]. Bioactive lipids are also potential biochemical markers of pain and inflammation[181] and metabolomics has been used to identify metabolic profiles that can differentiate between synovium samples from patients with OA and healthy individuals[182].

In 2006, the NIH-funded OA Biomarkers Network and the OARSI Clinical Trials Biomarkers Working group proposed a new classification system for OA biochemical markers termed BIPEDS[183, 184]. The purpose of this classification was to clarify the intended primary use of the biochemical marker to reflect Burden of OA disease, Investigative, Prognostic for OA development, Efficacy of OA intervention, Diagnostic for OA and Safety of intervention biochemical markers classification system for OA biochemical markers[183, 184]. However, a systematic review performed in 2010 concluded that individual biochemical markers and categories of biochemical markers, including their nature, origin and metabolism, need further investigation and validation[185]. In 2016, the FDA-NIH Biomarker Working Group published the BEST (Biomarkers, EndpointS, and other Tools) glossary[186]. The BEST resource aims to distinguish between biochemical markers and clinical assessments and to describe the distinct functions of biochemical markers in biomedical research, clinical practice, and medical product development. Harmonization of key terms by BEST avoids inconsistent use of key terms that can hinder the evaluation and interpretation of scientific evidence. BEST can thereby be expected to facilitate all aspects of biochemical marker work including testing, validation, commercialization, and perhaps even development for early OA.

Biochemical and molecular profiling of biological fluids (for example, serum, plasma and synovial fluid) and joint tissues can provide a global view of the physiologic state of an OA joint. Refinements in omics approaches and advances in analytical platforms and technologies will enable improved profiling of different stages of disease. To be clinically useful these biochemical markers need to be properly qualified (qualification is a regulatory process that links a biochemical marker with biomechanical and/or clinical outcomes) for early OA and they must adhere to the BEST guidelines to be effectively used in a clinical setting, rather than in an exploratory and hypothesis testing research setting.

Soluble biochemical markers require further study, validation, and qualification as susceptibility or risk outcomes for the development of early OA before being adopted for widespread use in the clinical care setting.

[H1] Conclusions

Various outcome domains exist that could be assessed for patients with early knee OA in research and/or clinical settings, including patient-reported outcomes, clinical features, measures of physical function, adiposity, physical activity or nutrition and biomechanical, imaging, or biochemical markers. Promising patient reported outcomes for this purpose include the KOOS and the ICOAP. Measures of physical outcomes (for example, single leg hop, quadriceps strength) and fat mass index (DXA) are also valid and reliable. With increasing popularity worldwide, a validated wearable physical activity monitor for quantifying levels of physical activity and a 3-day weighed food record for nutritional intake (for example, calories) has potential. MRI-defined OA and biochemical markers, although promising, require specific healthcare and research facilities where the assessment of these outcomes is possible and body fluids can be collected, stored and measured according to standard operating procedures. Additional considerations of patient-preferences and psychosocial outcomes are also important in future research examining early knee OA outcome measures[187]. In this regard, further patient-engaged research is recommended.

Importantly, multiple factors must be considered to facilitate risk assessment and the development of predictive models for early knee OA. Furthermore, definitions are needed for the potential outcomes, exposures, confounding and effect-modifying variables, duration of the clinically relevant prediction period and the setting in which the risk prediction tool will be used. As such, further research validating outcomes in individuals 'at risk' of early OA progression (for example, individuals with an intra-articular knee injury and/or who are obese) and 'early-OA' populations is required.

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Author contributions

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Competing Interests

CAE, JLW, AMa, NKA, KLB, CMT, RAR, DT, JLR, GK, DGL, TA, ME, VBK, EL, SBZ, JR, GP, FPL, LSM, MAR, AM, declare that they have no competing interests. E.M.R. and L.S.L declare that they contributed to the development of the Knee Injury and Osteoarthritis Outcome Score (KOOS). L.S.L. also declares that he contributed to the development of the ICOAP and the Anterior Cruciate Ligament Osteoarthritis Score (ACLOAS). AG is Consultant to Pfizer, TissueGene, AstraZeneca and Merck Serono. He is Shareholder of BICL, LLC. DJH is a Consultant to Pfizer, TissueGene, TLCBio and Merck Serono and contributed to the development of MOAKS.

Related links

KOOS scoring instructions: http://www.koos.nu/

Single Leg Hop for distance: https://www.sralab.org/rehabilitation-measures/single-limb-hop-tests

30-second Chair Sit-to-Stand Test: https://vimeo.com/74649743

6-minute walk test: https://vimeo.com/74649737

Box 1. Proposed outcomes for the assessment of early pre-radiographic OA

Below we provide suggestions for outcomes measures that could be used to assess individuals with early pre-radiographic OA in clinical practice and in research settings. Further research is needed, including evaluation of validity of early-OA specific outcomes and change in outcomes with progression of OA as many of these measures have been evaluated primarily in established OA[43, 44, 47-50, 57-59, 66, 153].

In clinical practice and research settings:

Patient-reported outcomes

The Knee Injury and Osteoarthritis Outcome Score (KOOS) can be used to measure pain during activity, other symptoms (e.g., stiffness, grinding, catching, swelling, knee flexion and extension, function in daily life and during sport and recreational activities, and quality of life across different age and treatment groups. The intermittent and constant assessment of pain score (ICOAP) can evaluate constant and intermittent pain

Clinical examination

A clinical assessment including joint line tenderness should be performed on individuals with newly-onset symptoms of knee pain, stiffness, crepitus, or a feeling of 'giving way'.

Functional outcomes

Three measures seem promising for use in clinical settings on the basis of their reproducibility, patient acceptability and the equipment[153] and expertise required: Single leg hop test[43, 44, 47-50], 30 second chair sit-to-stand[57-59], Star Excursion Balance Test[44, 51-56] and quadriceps strength measure[44, 47, 48, 52, 66]. Multiple additional functional measures have been validated for use in research settings.

Lifestyle-related outcomes

Adiposity can be assessed by body fat percentage or fat mass index (fat mass/height^2) using dual-energy x-ray absorptiometry or bioelectrical impedance analysis if available. BMI is more feasible in clinical settings, although has limitations for use in athletes. Levels of physical activity can be assessed using a validated physical activity monitor or a validated questionnaire if objective methods are not available. Nutrition outcomes are not currently suggested for use in routine clinical care, however the 3-day dietary record provides reliable estimates of nutrient intake.

In research settings only:

Biomechanical outcomes

Measures of biomechanical outcomes require further research and are not currently suggested for use in routine clinical care. However, such outcomes are ideal for informing the underlying mechanisms of OA progression and informing treatment interventions in research setting.

Imaging outcomes

The utility of plain radiography in early OA is limited. Although MRI has superior sensitivity to change and validity in the context of early OA [153], and is hence ideal in research settings, MRI is not thought appropriate for the routine clinical care setting because of the high cost and potential risk of over-diagnosis.

Biomarkers

No biomarkers are currently of use in routine clinical care; however, further validation of proteomic, lipidomic and metabolomic tools in research settings could lead to informative cartilage and synovial fluid profiles and provide important insights into OA progression.

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Table 1. Important physical function outcomes

Outcome measure	Test measure	Equipment Required	Reliability			Error	Validity		Responsive /Interpretability	Appropriate risk group (age)	References
			Intra	Inter	Re-test		Structural	Ho testing			
Single leg hop for distance	Length (cm)	Measuring tape	+	-	-	-	-	+/-	-	Post-trauma (≤45 years)	[43, 44, 47-50]
Cross hop for distance	Length (cm)	Measuring tape	+	-	-	-	-	+/-	-	Post-trauma (≤45 years)	[43, 47-50]
6 meter timed hop test	Time (sec)	Measuring tape	+	-	-	-	-	+	-	Post-trauma (≤45 years)	[43, 47-50]
Star excursion balance test	Length (% leg length)	Measuring mat, tape and skilled rater (leg length)	+	+	+	+	-	+	-	Post-trauma or obese (all ages)	[44, 51-56]
30-second chair sit-to-stand test	Count (# repetitions)	Chair and timer	+	+	-	-	-	-	-	Post-trauma or obese (all ages)	[57-59]
6 minute walk test	Length (m)	Flat 20m walking area, timer and chair	-	-	-	-	-	-	-	Obese (all ages)	[41, 42]
Vertical drop jump	Risk rating	31cm high box	+	+	-	-	-	+/-	-	Post-trauma (≤45 years)	[44, 60]
Single leg squat	Risk rating	None	+	+	-	-	+/-	+/-	-	Post-trauma or obese (all ages)	[44, 61-63]
Unipedal dynamic balance	Time (sec)	Balance pad and timer	-	+	+	-	+	+	-	Post-trauma or obese (all ages)	[44, 64]
20 meter shuttle run	Stage	Coloured tape and instructions.	-	-	+	+	-/+	+	-	Post-trauma (≤45 years)	[44, 65]
Quadriceps strength	Force (Nm/Kg)	Hand-held or isokinetic dynamometer and skilled rater	+	+	+	+	+	+	+	Post-trauma or obese (all ages)	[44, 47, 48, 52, 66]
Hamstring strength	Force (Nm/Kg)	Hand-held or isokinetic dynamometer	+	+	+	+	+/-	+/-	+/-	Post-trauma or obese (all ages)	[41, 43, 67]
Hip adductor or hip abductor strength	Force (Nm/Kg)	Hand-held or isokinetic dynamometer	+	+	+	+	-	+/-	-	Post-trauma or obese (all ages)	[41, 43, 67]

+ = supporting evidence, - = no supporting evidence, +/- = conflicting evidence

Box 2. MRI Defined Osteoarthritis (Hunter et al 2011)[161]

A definition of tibiofemoral osteoarthritis on MRI would be the presence of both group [A] features or one group [A] feature and two or more group [B] features Group [A] after exclusion of joint trauma within the last 6 months (by history) and exclusion of inflammatory arthritis (by radiographs, history and laboratory parameters): i) Definite osteophyte formation* ii) Full thickness cartilage loss Group [B]: 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
A definition of patellofemoral OA requires all of the following involving the patella and/or anterior femur: i) A definite osteophyte* ii) Partial or full thickness cartilage loss

* The definition of a 'definite osteophyte' was not delineated in the Delphi process and requires further validation.