Early-stage symptomatic osteoarthritis of the knee — time for action

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Abstract | Osteoarthritis (OA) remains the most challenging arthritic disorder, with a high burden of disease and no available disease-modifying treatments. Symptomatic early-stage OA of the knee (the focus of this Review) urgently needs to be identified and defined, as efficient early-stage case finding and diagnosis in primary care would enable health-care providers to proactively and substantially reduce the burden of disease through proper management including structured education, exercise and weight management (when needed) and addressing lifestyle-related risk factors for disease progression. Efforts to define patient populations with symptomatic early-stage knee OA on the basis of validated classification criteria are ongoing. Such criteria, as well as the identification of molecular and imaging biomarkers of disease risk and/or progression, would enable well-designed clinical studies, facilitate interventional trials, and aid the discovery and validation of cellular and molecular targets for novel therapies. Treatment strategies, relevant outcomes and ethical issues also need to be considered in the context of the cost-effective management of symptomatic early-stage knee OA. To move forwards, a multidisciplinary and sustained international effort involving all major stakeholders is required.

Osteoarthritis (OA) is the most prevalent joint disease, affecting over 500 million individuals globally, of whom more than 260 million have knee OA[1], representing a 9.3% increase from 1990 to 2017 (REF.[2]). In view of its major contribution to disease burden, we here focus on knee OA and the opportunities provided by defining and identifying persons with symptomatic early-stage OA of the knee. The term 'symptomatic' signifies the group of individuals seeking health care for their symptoms and who thereby differ from persons with risk factors for OA but without symptoms.

Management of OA should preferably aim to reduce the burden of the disease by changing its course to prevent long-term disability, but so far the efforts to do so have typically targeted patients in relatively late stages of the disease. Routine OA management is too often reactive rather than being proactive in identifying and treating patients in the early stages of the disease. Intervening early might stand a better chance of success, before the advent of chronic pain, severe joint destruction with biomechanical derangement, reduced function, disability and development of comorbidities[3–6]. Although the concept of early-stage disease is now embraced in many other chronic conditions such as diabetes mellitus, cardiovascular disease and Alzheimer disease[7–9], it also seems to be relevant for chronic arthritic diseases such as rheumatoid arthritis (RA)[10–12] and psoriatic arthritis[13]. A systematic review and meta-analysis of cohort studies and randomized controlled trials (RCTs) reporting outcome data of early RA supported the presence of a therapeutic 'window of opportunity', even when the heterogeneity of patients in the studies was accounted for[14].

The diagnosis and classification of symptomatic early-stage knee OA has been insufficiently explored and is yet to be agreed upon. Whether a window of opportunity exists for early-stage OA remains to be shown but, at least from the patient's perspective, early detection and intervention are relevant. The concept of early detection as a window of opportunity is supported by studies involving young patients undergoing surgical interventions for knee joint surface repair, such as autologous chondrocyte transplantation or implantation of an osteochondral scaffold, and early physical therapy interventions[3–5,15,16], as well as by the success of comprehensive management programmes in primary care such as Good Life with Osteoarthritis in Denmark (GLA:D®)[17]. To improve the chance of success in clinical studies that aim to slow disease progression and, importantly, ensure cost-effectiveness, stratification of the population with early-stage knee OA to identify those with an increased risk of disease progression will be required. Identification of people at the early stages of OA could also be helpful in limiting the long-term effects of the disease. As an example, a study in the Osteoarthritis

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Key points

- Early-stage knee osteoarthritis (OA) could present a 'window of opportunity' in which to arrest the disease process at the early stages and restore joint homeostasis.
- The initiating cellular and molecular cascade of events in early disease need to be studied in more detail and connected to triggering events and the patient profile.
- The goal of classification criteria for early-stage knee OA is to enable discrimination of patient populations with early-stage symptomatic knee OA, who are at increased risk of structural progression, from patients with knee symptoms due to other reasons.
- Final classification criteria for early-stage knee OA should be validated by a multidisciplinary panel of experts in the field with involvement of all relevant stakeholders.
- Early diagnosis in clinical practice enables proper disease management and reduction of the burden of disease.

Initiative (OAI) cohort suggested that the risks of experiencing a fall or fracture are higher (>50% and 85% greater, respectively) in people newly diagnosed with OA of the hip or knee compared with people of a similar age and characteristics without hip or knee OA[18].

The development of OA represents a continuum from health to the first presence of OA biomarkers — detected in body fluids or by non-invasive imaging, in the absence of clinically relevant symptoms/signs — then to symptomatic early-stage OA, established OA and finally end-stage OA (FIG. 1). While we acknowledge the process as a continuum, staging of it enables proper clinical management and research. In the 'at risk' stage and in the absence of clinical symptoms/signs, local or systemic molecular biomarkers or imaging biomarkers (for example, detected by MRI) could help identify patients at increased risk of developing full-blown knee OA. Patients with symptomatic early-stage knee OA typically present in primary health care with intermittent, activity-induced knee pain and/or discomfort[19], with limited or no radiographic changes. As the disease progresses, structural changes (such as osteophyte formation, joint space narrowing and subchondral bone sclerosis) become apparent and detectable on standard radiographs. At this stage, joint homeostasis has been lost, biomechanical derangement has occurred, and no approved treatment exists that can slow or reverse the disease process. Along with structural changes, the clinical symptoms typically worsen, with accompanying pain sensitization, and the disease manifestations become chronic. The presence of predisposing factors including family history of OA, previous knee injury and obesity can accelerate both symptoms and structural progression towards the later stages of the disease, which are defined by evident structural damage, pain and functional limitations, and other clinical complications[20].

The course of the disease is typically diverse and in an individual patient with OA is largely unpredictable. A substantial group of the OA population can follow a pattern of disease inertia; others worsen slowly whereas some follow an accelerated track[21,22]. Only a minority of all patients diagnosed with knee OA will ultimately undergo joint replacement surgery, but they nonetheless represent a sizeable and costly minority[23,24]. In the USA alone, the predicted annual count of total knee replacement procedures in 2020 is >1 million, and is predicted to increase by 400% by 2040 (REF.[25]).

Diagnosis of symptomatic early-stage knee OA provides the opportunity to manage the disease at an earlier stage with currently recommended first-line programmes. Indeed, despite the common perception of limitations in dealing effectively with knee OA[26], tools are now available to manage patients with knee OA, in particular in the early stages, and to reduce the disease burden[27,28]. These tools include, but are not restricted to, educational and exercise programmes, prevention of abnormal load or injury, approaches to enhancing coping strategies and managing expectations and, when needed, the addition of appropriate pain relief by use of local or systemic medication. Early-stage intervention also provides the opportunity to address the need for personalized lifestyle changes, including the promotion of exercise and weight control.

The accurate definition of early-stage knee OA by use of validated classification criteria would result in more homogeneous patient populations that would also enable better understanding of the mechanisms that drive the development of the disease. It would also facilitate interventional trials to validate therapeutic targets in the proper disease context and hopefully lead to therapies that can slow down joint destruction and even restore joint homeostasis. The development of the classification criteria discussed here are intended to serve as a 'first filter' to enrich for the patient population of interest; namely, those with early-stage knee OA. We expect that continued work by specialist groups will identify molecular and imaging biomarkers to further refine these classification criteria and/or enrich for patients at high risk of disease progression.

The purpose of this Review article is to assess the current best understanding of symptomatic early-stage knee OA and to highlight key knowledge gaps. These gaps most critically include optimized case finding, thus early diagnosis, in primary care, as well as defining symptomatic early-stage disease by use of classification criteria. We discuss treatment strategies and suggested outcome measures, and the ethics and risks associated with changing disease criteria as well as the need to align all stakeholders in this endeavour, including patients, health-care professionals, researchers, regulators and industry partners.

Diagnosis of early-stage knee OA

Diagnosis of early-stage disease focuses on case finding primarily in primary care, and proper management of the individual patient in clinical practice; this goal sits in contrast to that of classification criteria, which is to define early-stage disease with the aim of specifying homogeneous patient groups for clinical studies[29]. The diagnosis of early-stage knee OA is typically suspected when a chronic pattern of knee pain or discomfort develops over weeks to months, with periods of worse pain, stiffness and functional limitations for a week or more, interspersed with periods of little or no pain[30] (BOX 1). Clinical examination mostly reveals pain upon mobilization, joint-line tenderness, crepitus or mild joint effusion. Radiographic findings are of limited value in early-stage disease, as one of the typical features of OA — joint space narrowing — might not appear for many years[31].

The presence of Heberden's nodes, the bony swellings of the joint closest to the fingertips, is suggestive of generalized poly-articular disease[32] and has been associated with knee OA progression[32]. The diagnosis of early-stage knee OA can be further supported by the presence of risk factors such as older age, high body mass index (BMI), history of knee trauma or a family history of OA such as a history of joint replacement in first-degree relatives. Importantly, the absence of other differential diagnoses (for example, other arthritic diseases such as psoriatic arthritis and reactive arthritis) further supports the diagnosis of symptomatic early-stage knee OA. To date, to the best of our knowledge, no validated diagnostic criteria are available for early-stage knee OA. The Italian Society for Rheumatology has proposed a set of criteria for early symptomatic knee OA for the purpose of referral to rheumatologists, developed through a three-phase process comprising focus groups (including expert clinicians, researchers and patients), a systematic literature review and group discussions followed by a Delphi survey[33]; these criteria are yet to be validated. The CRiteria for the Early Diagnosis of Osteoarthritis (CREDO) group is working to develop a set of diagnostic criteria with relevance to primary care, using the Cohort Hip and Cohort Knee (CHECK) study cohort[34]. The latest report from this group, published in 2020, proposed three predictive models for the development of clinically relevant knee OA, as defined by experts; the first of these models was based on factors obtained from questionnaires and physical examination, the second model added radiographic factors and the third also included high-sensitivity C-reactive protein test. The predictive performance of these models was tested against experts' diagnosis of clinically relevant knee OA 5–10 years later, with the results indicating that the performance of all three models was 'fair' in making the distinction between cases with and without clinically relevant knee OA[34].

Classification criteria for early-stage knee OA

Classification criteria for symptomatic early-stage knee OA are needed in order to define more homogeneous patient populations for studies of epidemiology, natural

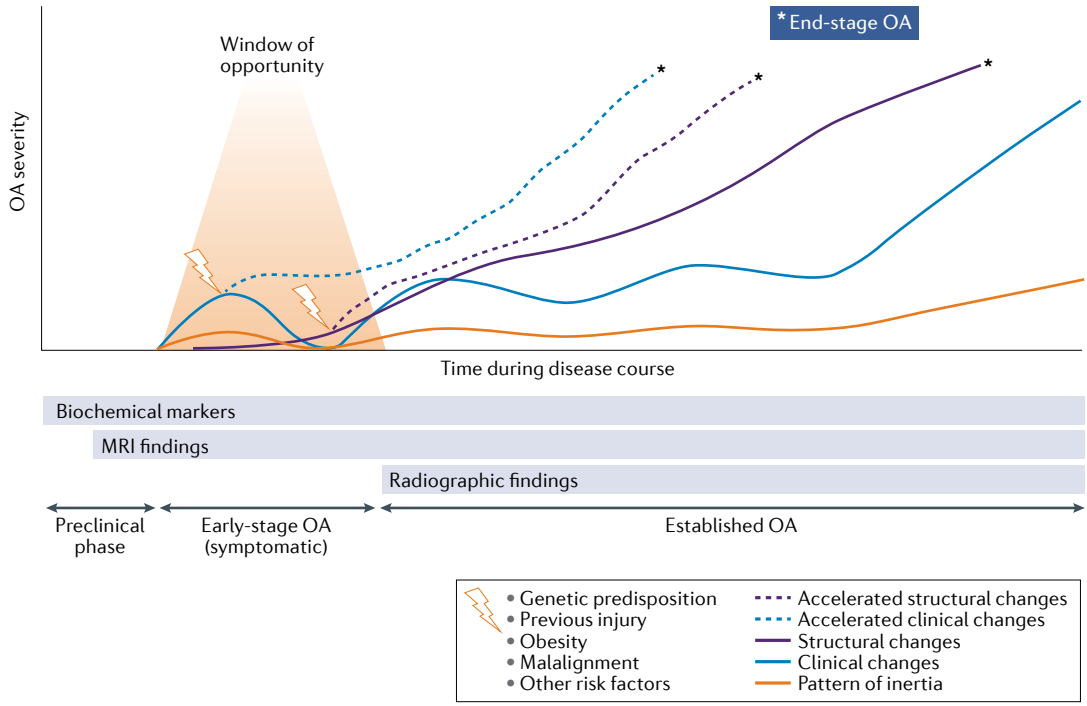

Fig. 1 | **The natural course of knee osteoarthritis.** This schematic presents the natural course of knee osteoarthritis (OA) from both clinical (blue line) and structural (black line) perspectives. The dashed lines signify the acceleration of clinical (blue) and structural (black) course of knee OA in the presence of predisposing (risk) factors for progression. The orange line presents the pattern of inertia. At the preclinical stage, some biomarkers (biochemical and MRI biomarkers) might be useful in identifying patients at increased risk of knee OA incidence. At the symptomatic stage of the disease, there are no or only limited radiographically detectable structural changes (Kellgren & Lawrence grade 0–1). People with early-stage knee OA typically present in health care with intermittent, activity-induced knee pain; this stage could serve as a 'window of opportunity' to arrest the OA disease process and restore joint homeostasis. As the disease progresses, structural changes (such as osteophyte formation, joint space narrowing, subchondral bone sclerosis and others) also become apparent and detectable on radiographs. At this stage, joint homeostasis is lost, biomechanical derangement often occurs, and the disease process thus becomes largely irreversible. Along with structural changes, the clinical symptoms also typically worsen with accompanying pain sensitization and develop towards chronicity. The presence of predisposing factors such as family history, previous knee injury and obesity, among others, could accelerate both clinical and structural progression towards end-stage disease, defined as evident structural damage, pain and functional limitations and/or other clinical complications. A minority of all patients diagnosed with knee OA will undergo joint replacement surgery, whereas a considerable part of the population of patients with OA follows a pattern of inertia.

Box 1 | **Diagnosis of symptomatic early-stage knee OA**

Pain pattern
- Chronic knee pain pattern developing over weeks to months
- Mechanical in nature increasing with loading and (over)use

Clinical features
- Joint line tenderness
- Crepitus or patellar grinding
- Mild joint effusion
- (Almost) normal range of motion

Radiographic findings
- Limited relevance in early-stage disease other than discrete bone remodelling or early osteophyte formation

Further supporting evidence
- Older age
- High body mass index
- History of knee trauma
- Family history of osteoarthritis (OA) (e.g. history of joint replacement surgery)
- Absence of other differential diagnoses

history and disease mechanisms and, importantly, for interventional studies. In contrast to diagnostic criteria, classification criteria typically aim to achieve high specificity and allow for lower sensitivity, and are thus less inclusive but more sharply defined[29]. The classification criteria should be reliable, universally applicable, clinically sensible and as precise as possible. The goal is to enable the discrimination of patients with early-stage symptomatic knee OA from patients with knee symptoms arising owing to other reasons, including acute knee injuries or other arthritic diseases. Further stratification of the subset of patients with early-stage symptomatic knee OA, for example by adding certain risk factors or by more comprehensive phenotyping, could enable enrichment of populations for patients whose knee OA will progress. This is a daunting task as no gold-standard definition of symptomatic early-stage knee OA exists, and even the existing classification criteria for established knee OA vary considerably[35,36]. The 1986 classification criteria[35] issued by the ACR (then known as the American Rheumatism Association) are the most frequently used. However, patients fulfilling the clinical and radiological ACR criteria for knee OA will already have considerable joint damage involving several tissues, such as cartilage, meniscus, underlying bone and synovium. A set of criteria for early-stage knee OA proposed in 2012 by the European Society for Sports Traumatology, Knee Surgery and Arthroscopy[37] bases classification on the presence of knee pain associated with degenerative changes detected by MRI or arthroscopy and is thus more targeted towards second-line health-care providers, typically orthopaedic surgeons and rheumatologists. A more recent set of criteria[38], proposed in 2018 by an international consortium, was designed to identify symptomatic patients with early-stage knee OA with a focus on primary care, as the majority of these patients are first seen by a general practitioner. These criteria rely on broadly applicable, simple, patient-based assessments and clinical examination in the absence (or near-absence) of radiological abnormalities (FIG. 2). The performance of the 2018 criteria in predicting structural and clinical progression of knee OA in the OAI population was encouraging, and the inclusion of additional clinical findings, such as presence of knee effusion and Heberden's nodes, improved the predictive performance of the originally proposed criteria[39]. This set of classification criteria has also been applied in other populations, for example, in the Iwaki Health Promotion Project cohort to investigate the prevalence and risk factors of early-stage knee OA in the Japanese general population[40–42]. Importantly, the use of validated classification criteria in future studies exploring biomarkers and other risk factors for early-stage knee OA would enable cross-study comparisons and meta-analyses. However, none of the proposed classification criteria sets have yet been validated. In order to do so, further comprehensive efforts are ongoing through a well-accepted four-phase process, which has previously been used in the development of classification criteria for other rheumatic diseases (FIG. 3). Thus, both data-driven and consensus-based, decision-science-informed approaches are being used to develop and validate a scoring system for symptomatic early-stage knee OA classification.

One of the challenges in developing classification criteria for early-stage knee OA is to exclude patients with knee pain due to other causes, in particular patients with chronic pain syndrome or related widespread pain syndromes such as fibromyalgia. Specific exclusion criteria, based on clinical expertise and/or validated questionnaires, are warranted.

Final classification criteria for early-stage knee OA should be proposed by a multidisciplinary panel of experts in the field, should include patients, and should result in validated criteria with the greatest content validity and construct validity. Such an ambitious project is ongoing and is guided by a multidisciplinary working group with observers from several relevant professional societies.

Risk factors and early-stage symptomatic knee OA

There is no indication that the risk factors for symptomatic early-stage knee OA would be much different than those for established knee OA.

The major risk factors for OA have been reviewed elsewhere[43], and include age (or years of exposure to any risk factor), overweight and obesity, joint trauma, high occupational joint loading, genetic susceptibility and, for women, menopause. On the basis of this list of factors, the presentation of a women who is postmenopausal, has overweight, has knee pain most days of the preceding month and has a history of repetitive knee (over) loading in the context of professional or recreational activities will prompt a clinician to suspect early-stage knee OA. If some additional non-modifiable risk factors are detected, such as a family history of knee replacement surgery, the clinician should assign this patient to a well-defined care trajectory.

ACR classification criteria for knee OA

Clinical and laboratory criteria	Clinical and radiographic criteria	Clinical criteria
• Knee pain At least five of the following: • Age > 50 years • Stiffness < 30 min • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth • ESR < 40 mm/h • RF < 1:40 • Synovial fluid analysis indicative of OA	• Knee pain • Osteophytes At least one of the following: • Age > 50 years • Stiffness < 30 min • Crepitus	• Knee pain At least three of the following: • Age > 50 years • Stiffness < 30 min • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth

Proposed classification criteria for early-stage knee OA

Using MRI or arthroscopic findings	Without MRI data

• Knee pain: at least two episodes of pain for >10 days in the past year
• Standard radiography: KL grade 0 or 1 or 2 (osteophytes only)
At least one of the following:
• Arthroscopy: ICRS grade I–IV in at least two compartments or grade II–IV in one compartment with surrounding softening and swelling
• MRI: at least two of the following:
  • At least grade 2 BLOKS for size of cartilage loss
  • At least grade 2 BLOKS for percentage full-thickness cartilage loss
  • Signs of meniscal degeneration
  • At least grade 2 BLOKS for size of bone marrow lesions
	• Patient-based questionnaires (KOOS): 2 out of the 4 KOOS subscales need to score 'positive' (≤85%)
	• Clinical examination: at least one of the following needs to be present:
	  • Joint line tenderness
	  • Crepitus
	• Radiography: KL grade 0–1 standing, weight bearing (at least two projections: posteroanterior fixed-flexion and skyline for patellofemoral OA)

Fig. 2 | **Comparison of newly proposed classification criteria for early-stage knee OA and the ACR classification criteria for knee OA.** Criteria for diagnosis and classification are related and could overlap in the features included, but diagnostic criteria focus on case finding and management of the individual patient in clinical practice whereas classification criteria aim to define disease with the goal of specifying homogeneous patient groups for studies of epidemiology, natural history and disease mechanisms and, importantly, for interventional studies. In contrast to diagnostic criteria, classification criteria typically aim to achieve high specificity and allow for lower sensitivity, and are thus less inclusive but more sharply defined. BLOKS, Boston Leeds Osteoarthritis Knee Score; ESR, erythrocyte sedimentation rate; ICRS, International Cartilage Repair Society; KL, Kellgren & Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; OA, osteoarthritis; RF, rheumatoid factor.

As yet, it is not possible to firmly establish the relative weight and/or ranking of OA risk factors, although overweight and obesity is reported to account for the single largest population-attributable risk[44,45]. More data are needed to construct a risk assessment tool such as those available for prevention and treatment of cardiovascular disease[46] and osteoporosis[47]. Risk assessment is also directly related to which outcomes are taken into account. For example, for reimbursement agencies, restoring function and returning to work might be the top priority, whereas from the patient's perspective, reducing pain and/or symptoms and maintaining function might be most important.

Although not intended for diagnosis, classification criteria for early-stage knee OA could also help with the identification of subjects at the early-stages of the disease, while detecting additional relevant risk factors could enable further stratification of early-stage knee OA patient subgroups with respect to specific phenotypes and management. For instance, OA in a relatively young (35–45 years old) man with a history of knee trauma and preceding surgical intervention, such as partial meniscectomy, is probably mechanistically distinct from that in a woman who is postmenopausal and has overweight aged 55–65 years old with a strong family history of bilateral total knee replacement. Therefore, these patients might be expected to respond differently to different treatments. For clinical trials aiming to slow or stop disease progression, criteria that enrich for those at highest risk of disease progression within the early-stage knee OA population are of importance. In that context, specialist groups are working to identify molecular and imaging biomarkers that could further refine the aforementioned classification criteria[48,49]. Such patient stratification could be a way of getting new drugs to market quickly as the intervention would reach the right patient in the right 'window' of the disease process, thereby increasing the chance of developing cost-effective treatments — an important requirement in the real world of limited health-care resources. These concepts have been proposed for other chronic diseases such as Parkinson disease[50].

Fig. 3 | **Development of validated classification criteria for rheumatic diseases.** The flow chart depicts the major steps in the ongoing process of developing and validating classification criteria for early-stage knee osteoarthritis. Such criteria sets have been developed for rheumatic diseases including rheumatoid arthritis[121,123,124], systemic sclerosis[125–128], systemic lupus erythematosus[129,130], gout[131–133], IgG4-related disease[134] and Sjögren syndrome[135].

Biomarkers in early-stage knee OA

In order to assess early-stage pathogenic events and develop appropriate biomarkers that reflect the early-stage processes in knee OA, it is critical to properly define early-stage disease and develop validated classification criteria widely accepted by the global community, so that all studies reflect a similar patient population and are comparable. Once early-stage disease has been well-defined, a better understanding of the cellular and molecular basis of the early disease processes in OA is crucial as this knowledge could enable us to identify the transition from a 'merely painful knee' to a knee with symptomatic early-stage OA disease.

No single unifying cellular or molecular cascade has been associated with the early disease processes, probably owing to OA typically being heterogeneous, also in its early stages[51]. The cellular and molecular events associated with early disease are diverse and are dependent on a number of factors, including those that initiate the disease, such as a single major trauma or a series of repetitive micro-traumata[52], inflammation[53] or infection. The initial disease processes act in a specific context that is influenced by patient characteristics such as unfavourable biomechanics[54], advanced age, genetic background and/or sex, and are modulated by comorbidities such as obesity and metabolic syndrome[55] (FIG. 4). Some of the molecular processes are catabolic and contribute to disease progression, whereas others are anabolic, which are of particular relevance in early disease and represent attempted or failed repair. As for the mechanisms driving early disease, a distinction has to be made between different patient populations and how their disease is initiated, as mentioned above. As an example, in post-traumatic knee OA events such as cell apoptosis, necrosis and premature senescence together with biomechanical overload can dominate[56–60]. In other patients with early-stage knee OA, angiogenic and metabolic changes with inflammation and involvement of the innate immune system could be of more relevance, and could be modified by age, sex and genetic background[61]. As another example, evidence is mounting that metabolic changes promoted by poor diet, obesity, ageing and comorbidities such as type 2 diabetes mellitus drive disease processes in chronic low-grade inflammatory diseases such as OA[55].

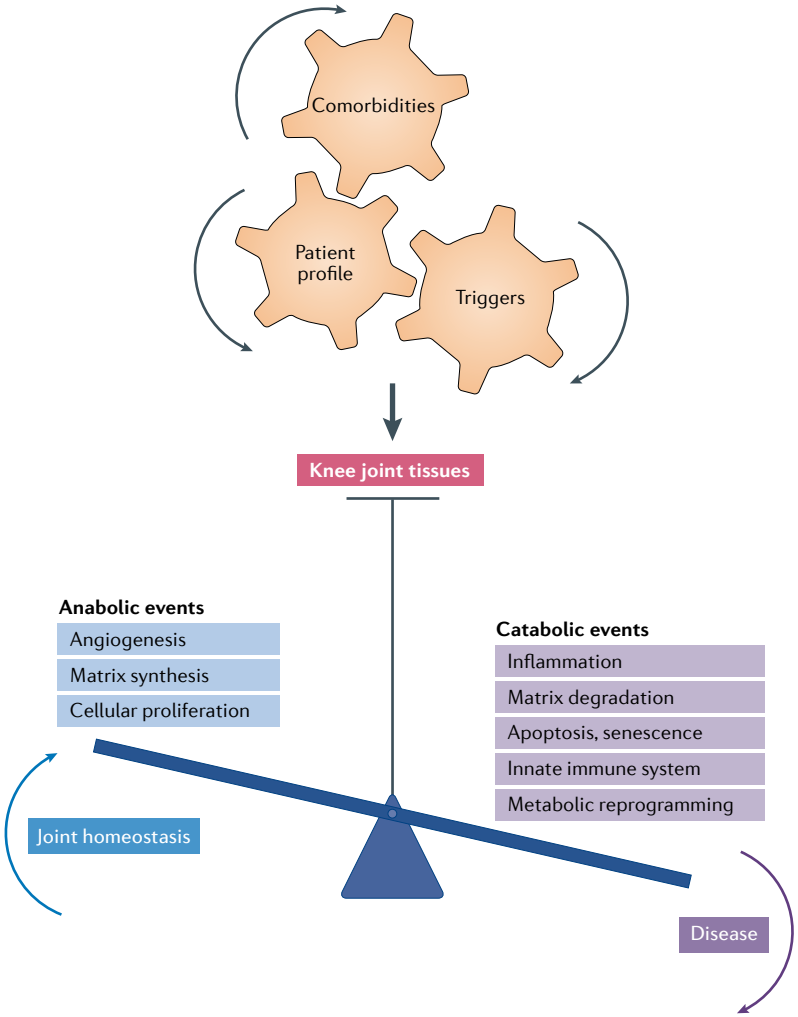

Fig. 4 | **Cellular and molecular events of early OA.** Triggering factors (for example, major trauma, repetitive minor trauma, inflammation, infection or altered biomechanics), patient profile (including characteristics such as sex, genetics, age, anatomy and history) and comorbidities (such as metabolic syndrome, obesity or diabetes mellitus) interact to affect all joint tissues in the knee, including the osteochondral unit, synovium, meniscus, infrapatellar pad and ligaments, resulting in activation of specific molecular cascades that lead to catabolic and anabolic events. Catabolic events include inflammation induced by several mediators such as damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs); matrix degradation by matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5); activation of the innate immune system mediated by macrophages, Toll-like receptors and complement activation; metabolic reprogramming; and senescence. Enhanced anabolism is mediated through the activation of mostly developmental pathways, such as transforming growth factor β (TGFβ)–bone morphogenetic protein (BMP) and fibroblast growth factor 2 (FGF2) signalling. When anabolic events are successful, joint homeostasis is restored; when catabolism is overwhelming, the disease process becomes chronic and probably irreversible. OA, osteoarthritis.

Further stratification of early-stage knee OA might require the use of biomarkers based on aetiopathogenic insights. Besides contributing to defining the stage of the disease process, biomarkers can serve additional purposes, such as identifying patients at increased risk of progression from an early-stage disease process to established OA[62].

Biomarkers can be divided into molecular and imaging biomarkers[63], the latter mainly related to MRI. A detailed discussion of potential biomarkers is outside the scope of this Review, but a brief view is provided below; the reader is referred to several reviews published in the past few years for further discussion of this topic[48,49,64,65].

Molecular biomarkers are typically measured in body fluids such as serum, urine or synovial fluid, and can reflect systemic processes or local, joint-specific processes. For early-stage knee OA, we would anticipate that synovial fluid is probably the body fluid most reflective of the local processes in the joint, as any systemic effect of the OA disease process might not yet be detectable. Considerable efforts to identify molecular biomarkers by the 'candidate protein' approach have had limited success in identifying and qualifying biomarkers that are useful in the clinical or trial setting.

Renewed efforts using a genome–proteome–metabolome-wide-association approach are ongoing[66]. Both approaches are handicapped by our limited understanding of how best to identify OA subpopulations with regard to genotype, phenotype, risk factors and more. Following the discovery of a promising biomarker comes assay validation and then qualification to confirm the clinical utility of the biomarker using retrospective then prospective human cohorts. One of the major challenges with the use of molecular biomarkers is to ensure their robustness and reproducibility at a relevant scale in different populations, different settings and different laboratories. Unfortunately, many candidate biomarkers seem not to provide much additional value beyond that of the known risk factors[67,68].

Imaging biomarkers include features of MRI and ultrasonography for diagnosing or classifying early-stage OA[69].

Box 2 | **Core outcomes for early-stage knee OA**

Currently available clinically relevant outcomes
- Patient-reported outcomes (e.g. KOOS, ICOAP questionnaire)
- Clinical features (e.g. joint line tenderness, crepitus, effusion)
- Lifestyle-related features (e.g. BMI)
- Structural features (e.g. knee radiograph features)

Potential clinically relevant outcomes
- Physical activity monitored using wearable devices

Outcomes of use for research purposes
- Imaging biomarkers (e.g. ultrasonography and MRI biomarkers)
- Molecular biomarkers

BMI, body mass index; KOOS, Knee Injury and Osteoarthritis Outcome Score; ICOAP, Intermittent and Constant Osteoarthritis Pain; OA, osteoarthritis.

Ultrasonography lacks clear findings in early-stage OA but has some potential to non-invasively detect aspects of the joint tissues that can indicate active disease, such as the presence of effusion or synovitis. However, results of a 2017 study indicate that examination by ultrasonography is no more sensitive than clinical examination by appropriately trained clinicians[70]. Meniscal pathology can be partially detected, specifically meniscal extrusion, but meniscal abnormalities can be much better defined and detected on MRI.

MRI has great potential with respect to imaging biomarkers for early-stage knee OA and has been discussed in detail elsewhere[71]. However, MRI still has limitations, including a lack of understanding of what particular MRI findings represent at the tissue, cellular and molecular level, for instance, the processes underlying subchondral bone abnormalities[72]. Another hurdle is the great sensitivity of MRI and the difficulty of distinguishing pathological and clinically relevant findings from what can be regarded as normal joint tissue remodelling and ageing[73,74]. Suffice it to say, this technology could help to detect the effect of an intervention at the tissue level, but the clinical relevance, or how it affects the course of the disease process and its progression, is still to be investigated in detail and agreed upon.

Outcomes of early-stage knee OA

When defining a patient population with early-stage OA, and thus intrinsically creating a new class of patients, it is essential to define appropriate outcomes for these patients. A 2019 review presented and discussed an extensive list of potentially relevant outcomes[65]. With respect to early-stage OA, an ambitious outcome would be full 'remission' or 'minimal disease activity', outcomes also used for other arthritic diseases such as RA[75]. This state can be defined in several ways, for instance as restoration of joint homeostasis at the molecular level with the disappearance of abnormalities detected by imaging with sensitive tools such as MRI and, from the patient perspective, as the absence of pain, discomfort, symptoms or signs and restoration of function. That outcome is the ideal, of course, but by creating a category of patients with early disease, we should aim for that. Alternatively, as has already been done for inflammatory arthritis[76], we could define 'very low disease activity' for patients with OA, potentially measured by use of outcome tools such as the Knee Injury and Osteoarthritis Outcome Score (KOOS) or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Objective assessment of joint function also seems appropriate and methods to do so have been presented[65]. Also of interest are dynamic functional assessments using wearable monitors, as these devices can document real-life performance in activities of daily living as well as in professional and recreational life[65,77].

For interventional trials, it is important to define the changes required to claim that a drug has disease-modifying activity and could thus be considered a disease-modifying osteoarthritis drug (DMOAD)[78,79]. In early-stage knee OA, radiographic findings on plain radiographs are minimal, and demonstrating disease progression in this regard requires large numbers of patients over long time periods, typically 3–4 years or more. Other imaging technologies such as MRI and refinements thereof could be valuable in this context[71]. Adaptive trial designs that enable patient subgroup enrichment can be considered[80]. As an example, subgroups of patients with early-stage knee OA who are at a high risk of structural progression can be selected on the basis of having Kellgren & Lawrence grade I on radiographs, as these patients will have a much higher risk of developing Kellgren & Lawrence grade II with osteophytes and joint space narrowing (a sign of established OA) than patients who have no radiological abnormalities[39,81] Using an adaptive trial design, initial treatment of different subgroups of patients with early-stage knee OA can be followed by interim analysis, after which only subgroups that benefit from the treatment are randomly allocated to receive further treatment or placebo and the other groups are dropped or re-assigned to alternative trial arms. Investigations using machine learning and MRI-detected bone-shape changes found that this measure is far more sensitive to change than plain radiograph scores[82], suggesting that novel DMOAD trial designs could become feasible with the use of more advanced imaging strategies. Demonstration that an intervention has positive effects on symptoms and functional outcomes superior to those of placebo for the entire study population, in combination with showing a structural benefit for a high-risk subgroup, could justify the highly sought after 'DMOAD' label. Stakeholders in the field need to reach consensus and set the standards for outcomes of early-stage knee OA (BOX 2).

Management strategies

Knee pain is common among those aged over 50 years, and a very variable proportion of these individuals are assigned a diagnosis of knee OA when seeking health care or being examined in population-based studies[83,84]. On continued follow-up, one-quarter to one-third of those originally assigned as having 'only' knee pain received a diagnosis of knee OA[84,85]. There is thus a clear need to reduce variation in diagnosing both knee OA

and early-stage knee OA, and to understand the consequences for the patient who has symptoms but does not receive a diagnosis, in terms of missed early opportunities for best management of OA. For the symptomatic patient, a missed diagnosis represents a missed opportunity.

In the initial attention to early-stage disease, the focus should be on reducing the burden of disease through identifying in the routine clinical setting persons with knee symptoms and increased likelihood of early-stage OA, and to treat them with the tools available now[28]. If implemented and applied to the right patient, best practice disease management can reduce the burden of the disease, and might even affect disease progression[15,27,28,86].

No evidence has been presented on which to base best management specifically for patients with symptomatic early-stage OA. Logic suggests that the preferred treatment should be the first-line management approach recommended for almost any patient with knee pain and OA: a structured programme of education, information and exercise, and weight loss when needed[87,88]. Published results show that this management approach is beneficial both for those with mild symptoms and for those with more severe symptoms, and is associated with reduced pain and consumption of analgesics, less sick leave, better quality of life and function and increased physical activity[89,90]. Although evidence of the effects of exercise and lifestyle modification on OA-related joint structural integrity remains limited[91,92], the reductions in pain, consumption of analgesics and sick leave at the population level has the potential to importantly reduce the OA burden[15,17,86,90–92]. The societal advantage gained might be as important as that from decreasing the need for joint replacement in more severe stages of OA.

Exercise might potentially affect the disease process, including in early-stage OA[15,86], but limited implementation and patient compliance remain major hurdles[93–96]. Initiatives have been developed to overcome some of these hurdles, such as the Better Management of Patients with OA programme[91] and the GLA:D® programme for people with knee and hip pain[92]. The GLA:D® project is an outstanding example of how to successfully implement evidence-based clinical guidelines in primary health-care practice. Its underlying principles focus on patient education, patient empowerment, exercises and self-management and routine documentation of outcomes. This project now serves as a template for establishing similar initiatives in other countries including Australia, Canada, China, New Zealand and Switzerland[17]. To expand the reach, implementation and cost-effectiveness of these first-line management principles for OA, digital tools have been introduced[90]. A low-cost, low-tech, low-risk early intervention strategy such as this requires the identification of patients with early-stage disease and proper patient stratification. Tools are available to the caregivers to do so, but so far are poorly implemented[26,93,95–102]. From the patient's perspective, quality of life remains affected and more attention by caregivers is required[103]. Establishing a proactive case-finding strategy for symptomatic early-stage knee OA, identifying those patients at risk of disease progression and designing a care trajectory supported within primary care represents a major opportunity to reduce the globally heavy disease burden of OA. The unfortunate defeatist perception exists that OA is a disease for which nothing can be done other than alleviating the symptoms. This bias arises from our often drug-driven health-care system and the fact that no DMOADs are yet available. The past failure to develop DMOADs is due to many factors, including the complexities of the disease process and disease stages, the heterogeneity of the patient population and that translational animal models seem to incompletely predict the outcome of treatments in humans. A better understanding of the cellular and molecular processes of the distinct disease stages in the OA patient, patient stratification based on scientific insights and the use of model systems that reliably predict outcomes in human patients could help us move forwards in the quest to affect disease development and delay progression (BOX 3). The design of interventional trials in early-stage disease will be no less challenging than in previous (failed) trials with disease-modifying ambition[78,79]. The continued development, validation and qualification of biomarkers will be critical to identify and monitor early-stage OA in clinical trials.

Stratification of the OA population to identify persons with early-stage symptomatic disease combined with a high risk of disease progression could present an attractive target to influence disease development before the advent of chronic pain, secondary processes and severe joint destruction. Drugs are in development that have articular

Box 3 | **Research gaps and proposed agenda**

Existing gap
To date, no validated diagnostic criteria are available for early-stage knee osteoarthritis (OA).

Proposed research agenda

- Develop diagnostic criteria or validated tools for the diagnosis of early-stage knee OA with the aim to properly manage the individual patient, in particular in primary care.

Existing gap
The definition of symptomatic early-stage knee OA has been insufficiently explored and is yet to be agreed upon. The 1986 classification criteria by the ACR are the most frequently used, but patients fulfilling the clinical and radiological ACR criteria for knee OA will already have significant joint damage.

Proposed research agenda

- Develop and validate classification criteria for early-stage OA to define homogeneous patient groups for clinical studies.

Existing gap
By defining early-stage knee OA, a new class of patients are being created; it is essential to define the most appropriate outcomes for these patients.

Proposed research agenda

- Identify and validate outcome measures associated with early-stage OA.

Existing gap
Insufficient understanding of the early-stage disease processes.

Proposed research agenda

- Investigate underlying cellular and molecular mechanisms driving the development of early-stage OA and OA progression.
- Identify potential biomarkers (wet or dry) of early-stage disease and associated with disease progression.

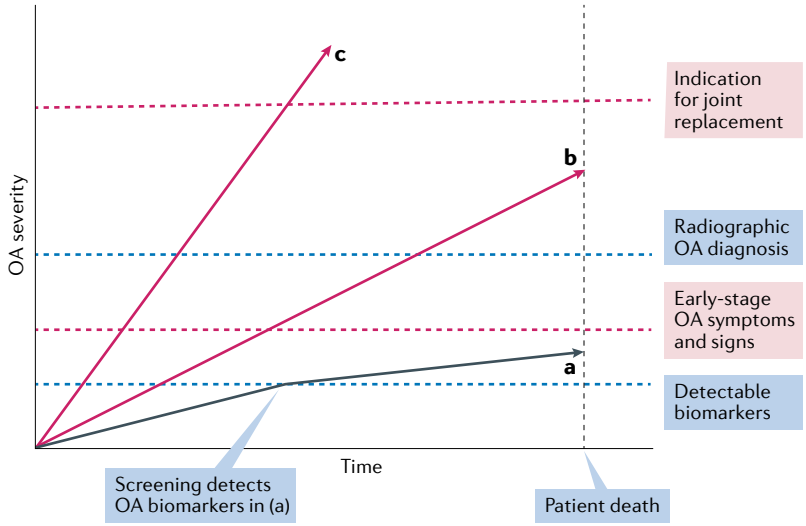

Fig. 5 | **The potential for overdiagnosis and overtreatment of OA.** In this schematic, the vertical axis represents 'global' osteoarthritis (OA) disease severity and the horizontal axis represents time (and patient age). The two horizontal dashed red lines represent the degree of severity (disease stage) at which symptoms begin, or become so severe that joint replacement surgery may be indicated. The lower horizontal dashed blue line represents the disease stage at which biomarkers (MRI or molecular biomarkers) might first detect an increased risk for disease, and the upper horizontal dashed blue line when a diagnosis of radiographic OA can be made using plain radiography. The vertical dashed line represents the time at which death could take place. The arrows labelled a, b and c represent OA disease trajectories with different rates of disease development. In this schematic, individuals along trajectory a, whose disease progresses slowly or not at all, would be over-diagnosed by biomarkers; they would never experience symptoms and any treatment would be overtreatment. Individuals along trajectories b and c could benefit from both having their symptoms recognized as early-stage OA and receiving beneficial symptomatic treatment before the point at which a radiographic diagnosis would be made. Future research could show whether OA treatment at this early stage can modify the development of further symptoms and structural joint changes for individuals along trajectories b or c, thus providing OA disease modification.

cartilage or other joint tissues as primary targets[104–106]. Published results at the time of writing this Review suggest that some of the novel compounds in development might influence joint structure, but this effect has not yet been shown to translate into a proven effect on patient symptoms. A comprehensive review of new drug studies is outside of the scope of this review but has been discussed elsewhere[107].

An alternative strategy to prevent disease progression in early-stage OA involves regenerative medicine. There is interest in the intra-articular injection of stem cells for the treatment of knee OA, and some interesting results have been described but there is a clear lack of pivotal, high-quality clinical studies[108,109]. Other approaches involve the use of gene therapy or a combination of cell therapy and gene therapy by intra-articular injection into the knee joint of engineered cells that carry viral and non-viral vectors expressing growth factors[110–113]. Tissue engineering solutions are attracting attention; deep osteochondral lesions are a clear risk factor for developing OA, and some promising approaches to osteochondral repair have been reported[114]. However, better evidence is needed from more rigorous RCTs, preferably using placebo surgery controls[115].

For the patient with knee pain suggestive of early-stage OA seeking primary care, of central importance is clear communication with the patient about what is causing the symptoms, what to expect and what can be done and, importantly, what can prevent progression to chronic pain and sensitization[6,116].

Overdiagnosis, overtreatment and ethics

By introducing the concept of symptomatic early-stage OA for patients with knee symptoms and signs — akin to 'proper, established' OA but without most of the classical radiographic changes — the current disease definition for OA is expanded. With redefining the disease comes the risk of overdiagnosis and overtreatment, and of being seen as acting in self-interest and the interests of industry[117] (FIG. 5). Concern might also be raised about the creation of a new disease that lacks an effective treatment. However, as discussed in this Review and other efforts for early case-finding, the focus should be on people who seek health care because of knee symptoms and who, in a clinical consultation, can be diagnosed with high likelihood as having early-stage knee OA. The majority of these patients can be successfully managed with existing first-line treatments including education, structured exercise programmes, weight loss (when needed) and add-on pain relief, for example with intermittent, low-dose NSAID, when indicated[87,92,118].

Continued research on genetics, biomarkers, and cell and tissue processes active in the earliest stages of OA could lead to the identification of individuals at-risk of OA before they develop any symptoms. However, identifying and possibly treating those at risk but without symptoms raises broad concerns of overdiagnosis, overtreatment, the number needed to treat to prevent one case of symptomatic disease, and cost (FIG. 5).

Conclusions

Management of the high burden of knee OA remains a major public health challenge, with no disease-modifying drug treatments available. Efforts in the field should focus on future opportunities, drawing on past experience and on strategies that have already been successfully pursued and implemented for the management of other chronic diseases incorporating new and innovative technologies. This entails basic research to identify new mechanisms of disease as potential treatment targets. Noting that past bench-to-bedside translational research with the aim of bringing DMOADs to the market has met with limited success, an increased focus on the human clinical disease and its subtypes and adapting management approaches and trial designs seem paramount.

OA is a heterogeneous disease and in a minority of patients leads to joint failure that requires joint replacement, a procedure still considered the most important 'breakthrough' treatment in OA. The disease heterogeneity slows progress in research and treatment. Compounding this problem is the unpredictable course of the disease, elegantly described as a state of inertia[21], and the challenge of identifying factors that trigger the transition from stable disease to disease progression.

In view of these challenges, disease stratification seems to be a prime goal[119]. Among stratification strategies,

detecting and defining early-stage disease could present a 'window of opportunity' as already illustrated with notable effects in patients with RA[120,121].

As well as ongoing research to diagnose early-stage disease in primary care, efforts to develop and validate classification criteria for symptomatic early-stage knee OA[38] are summarized in this Review. Such criteria will serve to define more homogeneous patient populations for clinical studies, and will help us to better understand the mechanisms of disease and provide a sound scientific basis for the development of new disease-modifying therapies. The corresponding clinical diagnosis helps to identify the patient in primary care, thus providing them with access to appropriate, proactive disease management. However, caution is also advised, as overdiagnosis and overtreatment is a risk[122], in particular when new drugs or other interventional or surgical therapies enter the market.

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Author contributions
A.Ma., L.S.L., A.Mo. and F.P.L. researched data for the article. All of the authors made substantial contributions to discussions of the content, writing the article and reviewing and/or editing of the manuscript before submission.

Competing interests
L.S.L declares that he serves as member of an AstraZeneca Data and Safety Monitoring Board, has acted as a consultant for the planning of phase II and III clinical trials for Paradigm Biopharmaceuticals Australia & Ireland, is a member of an expert group for assessing research proposals on musculoskeletal pain for Pfizer/Lilly USA, acts as a consultant for the scientific evaluation and publication of outcomes of an eHealth app for hip and knee osteoarthritis (Arthro Therapeutics Sweden), and was a member of an expert group for National Guidelines Osteoarthritis Care 2020 for the National Board of Health and Welfare Sweden. A.Mo. declares that he has acted as a consultant for Abbvie, AlphaSights, Artialis SA, Atheneum Partners, Flexion Therapeutics, Galapagos, GSK Consumer Healthcare, Guidepoint Global, Image Analysis Group, Kolon TissueGene, Novartis, Pacira Biosciences Inc, Pfizer Consumer Healthcare, Servier, Sterifarma, and Science Branding Communications; has received research funding from the European Commission (FP7, IMI, Marie Skłodowska-Curie, ES Struktūrinės Paramos), Versus Arthritis (Arthritis Research UK) and initiated research contracts with Merck KGaA and Kolon TissueGene; he has received speaker payments from Achē Laboratórios Farmacêuticos, the American College of Rheumatology, Bioiberica SA, the Korean Society for Osteoarthritis and Cartilage Repair, Laboratoires Expanscience, the Spanish Society of Rheumatology, Sanofi, the Heilongjiang Rheumatology Association and the Zhujiang Hospital of Southern Medical University; he currently serves as President of the Osteoarthritis Research Society International (OARSI), a member of the Advisory Board of Research Square and he is a member of the Scientific Advisory Board of Kolon TissueGene; however, none of the organizations listed above was involved in the conceptualization, design, data collection, analysis, decision to publish, or preparation of this manuscript. M.E. declares that he has received an honorarium for serving on a 1-day advisery board for Pfizer; he also serves as an Executive Board Member (Treasurer) for OARSI. A.Ma. and F.P.L. declare no competing interests.

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