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Osteoarthritis

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Abstract

Osteoarthritis is a heterogeneous whole-joint disease that can cause pain and is a leading cause of disability and premature work loss. The predominant disease risk factors – obesity and joint injury – are well recognized and modifiable. A greater understanding of the complex mechanisms, including inflammatory, metabolic and post-traumatic processes, that can lead to disease and of the pathophysiology of pain is helping to delineate mechanistic targets. Currently, management is primarily focused on alleviating the main symptoms of pain and obstructed function through lifestyle interventions such as self-management programmes, education, physical activity, exercise and weight management. However, lack of adherence to known effective osteoarthritis therapeutic strategies also contributes to the high global disease burden. For those who have persistent symptoms that are compromising quality of life and have not responded adequately to core treatments, joint replacement is an option to consider. The burden imparted by the disease causes a substantial impact on individuals affected in terms of quality of life. For society, this disease is a substantial driver of increased health-care costs and underemployment. This Primer highlights advances and controversies in osteoarthritis, drawing key insights from the current evidence base.

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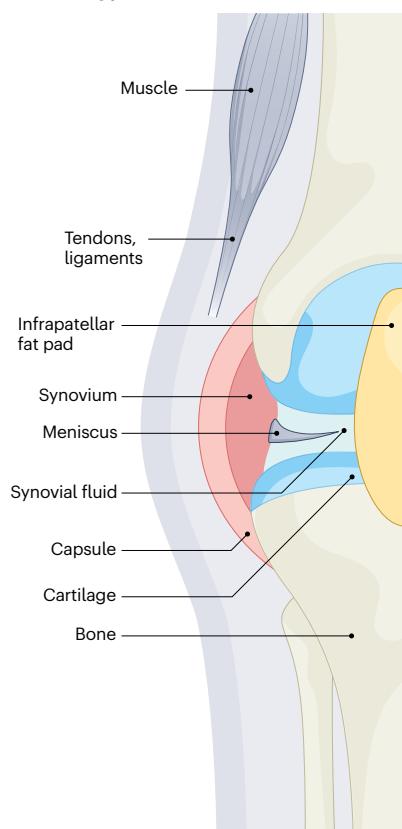
Introduction

Osteoarthritis (OA) is a serious chronic condition and a leading cause of disability, affecting over 500 million people worldwide¹. Once regarded as a simple ‘wear and tear’ or ‘degenerative’ joint disease, OA is now understood as a complex, multifactorial disorder affecting the entire joint, including the bone, cartilage, ligaments and muscles^{2,3} (Fig. 1). The modern definition endorsed by The Osteoarthritis Research Society International (OARSI) defines OA as a disorder of movable joints marked by cell stress and extracellular matrix degradation⁴. This condition is often initiated by major or micro trauma to the joint, which can subsequently lead to joint tissue metabolism abnormalities, progressing to anatomical and physiological disruptions such as cartilage degradation, bone remodelling, osteophyte formation and joint inflammation. These pathological changes eventually lead to the loss of normal joint function and culminate in pain and disability. While this definition framework primarily applies to knee and hip OA, it is adaptable to hand OA, and modifications are still required to accurately define OA in other joints. Importantly, it is crucial to distinguish between OA as a disease, characterized by pathological changes in joint tissues and structural alterations, and OA as an illness, which is predominantly marked by symptoms such as pain and disability. These symptoms are what typically compel individuals to seek medical intervention, highlighting the critical need to address the illness of OA early in the disease course when symptoms are typically episodic by targeting the leading modifiable risk factors to mitigate its extensive impacts on individuals and the wider society⁵.

This evolving perspective underscores the need for a global reassessment of OA, shifting from a narrative of inevitable decline to one that recognizes the dynamic and multifactorial nature of the disease, thereby informing more effective management and therapeutic strategies⁶. This shift is particularly important in the context of early-stage symptomatic knee OA, where there is a growing recognition of the need to identify and intervene at this early phase of the disease and to distinguish it from late-stage OA⁷. Efforts are under way to establish validated and widely accepted classification criteria for early-stage OA, attempting to identify the disease at a stage where interventions could more effectively restore joint homeostasis and slow or halt OA progression⁸. In addition, efforts led by the Late-stage Knee and Hip Osteoarthritis Composite Measure Working Group are ongoing to define a clinical end point for late-stage OA, driven in part by clinical trial needs and calls from regulators, and aiming to aid in the assessment of whether total knee or total hip replacement is required. The receipt of total joint replacement is also dependent on a range of factors other than the illness, including access and preference for surgery and social, economic and geographical factors.

OA prevalence continues to increase unabated in part due to the changing societal demographics, with increasing numbers of older adults with obesity. The leading risk factors for disease – obesity and joint injury – are both eminently modifiable. Still, at this point, little is done to address these either from a primary or secondary prevention perspective. In contrast, age and sex also play important roles as disease risk factors but they are not modifiable.

a Healthy joint



b Osteoarthritic joint

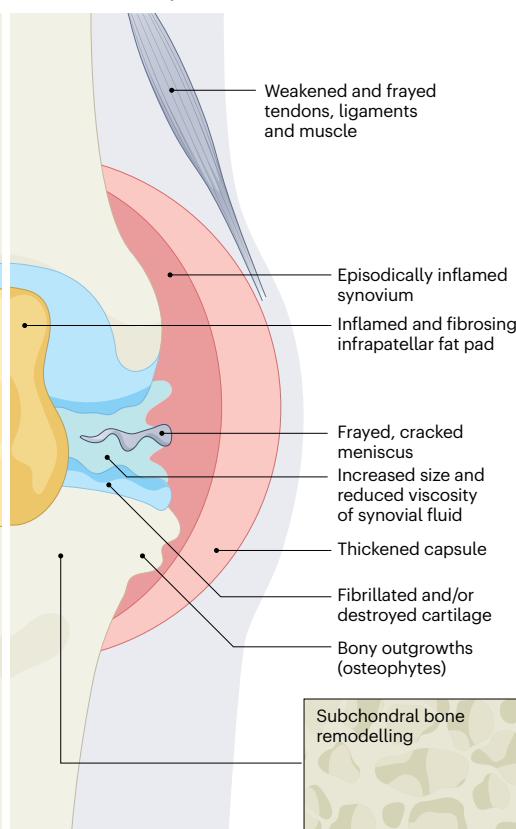


Fig. 1 | Healthy and osteoarthritic joint. This figure shows the healthy joint (part **a**) and osteoarthritic joint (part **b**). Almost all tissue structures in osteoarthritis joint tissues show pathological changes, including articular cartilage degradation, fibrosis and inflammation of the synovium and infrapatellar fat pad, subchondral bone remodelling, meniscal damage and ligament damage. Adapted from ref. 2, Springer Nature Limited.

Our understanding of the pathogenic changes occurring in OA is that they are dynamic and reflect an imbalance of catabolic and anabolic processes favouring disease. We recognize OA as a whole-joint disease, with involvement of the entire joint and its constituent tissues, not just cartilage. The heterogeneity of OA disease presentations and mechanisms involved is being recognized, including an evolving literature on the OA phenotypes and the pathogenesis of pain.

Despite the tremendous burden OA places on individuals, families, health-care systems and society, the care that patients with OA receive is often fragmented, of low value and inappropriate⁹. Our reactive health-care system incentivizes and subsidizes expensive investigations and interventions of little or no benefit, including frequent use of magnetic resonance imaging (MRI) to establish a diagnosis that can be made clinically based on symptoms and signs, or recommend arthroscopy, an intervention proven to be of no benefit but with substantial costs and potential harms. In contrast, current evidence-based management strategies advocate a focus on the alleviation of symptoms through lifestyle interventions such as exercise, physical activity, and weight management or weight loss³.

In this Primer, we highlight recent advances in our understanding of OA disease and its management. We focus on the epidemiology, pathophysiology, diagnosis, management and burden of the disease. We provide a perspective on the outlook of the field and suggest directions for key research questions.

Epidemiology

Incidence and prevalence

OA affects various body sites, each site with differing frequencies (Fig. 2) and impact on the individual's mobility and quality of life. The knee is the most affected site, also facing the highest burden of OA due to its weight-bearing function and exposure to mechanical stress. Approximately 45% of individuals may develop symptomatic knee OA over their lifetime¹⁰. The hip and hand joints also show notable OA prevalence, with hip OA more common in older adults (7.34%, aged ≥30 years) and contributing to severe disability¹¹. Hand OA affects the small finger joints and the thumb base and is typically seen in middle-aged and older individuals, particularly women (44.2% in women versus 37.7% in men)^{12,13}. The spine, especially the cervical and lumbar regions, is another critical area affected by OA, significantly influencing daily activities and work capacity¹⁴. Although less common, ankle and shoulder OA can be particularly debilitating^{15–17}. Elbow, wrist and temporomandibular joint OA are also less frequently seen^{16,18,19}.

OA is the most prevalent form of arthritis and significantly impacts global health demographics. In 2020, an estimated 7.6% of the global population, equating to approximately 595 million individuals, were living with OA²⁰. This represents a substantial increase from 1990, when 4.8% of the global population (256 million individuals) were affected. In 2020, 14.8% of the global population aged 30 years or older experienced some form of osteoarthritis. Among adults aged 30–60 years, who are considered to be of working age, 3.5% were affected. Since the 1990s, the prevalence and incidence of early-onset OA (that is, diagnosis of OA before age 55 years) have increased²¹.

The incidence of OA escalates with age, influenced continuously by biomechanical stress and systemic factors such as obesity and metabolic syndrome. These might start impacting joint health much earlier in life but become significantly pronounced after the age of 50 years, reflecting the cumulative impact of these factors over time. Women are particularly susceptible, reflecting biomechanical and hormonal changes at post-menopause, although the direct causal

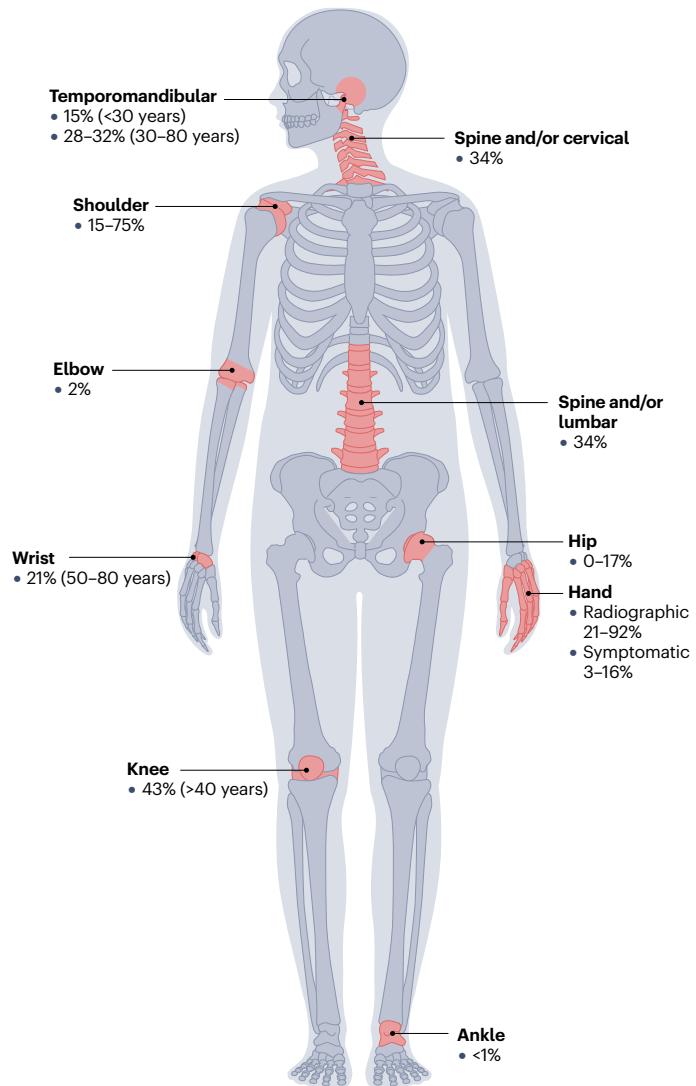


Fig. 2 | Common osteoarthritis sites. Prevalence of osteoarthritis by anatomic region. Percentages indicate the proportion of the population affected within specified or available age ranges. Where age-specific data are available, they are indicated below each anatomical site. In regions without specified age data, comprehensive age-related prevalence figures were not uniformly available across sources. Data from refs. 13,15–19.

link between menopause and OA remains under ongoing investigation and debate²².

The highest age-standardized prevalence rates are observed in high-income regions in Asia Pacific and North America, while the lowest rates are detected in Southeast Asia and sub-Saharan Africa, indicating significant global disparities that should influence regional public health strategies²⁰. Of note, these observations derive from the Global Disease Burden study and might reflect compositional biases as the majority of data originates from high-income areas, which could potentially skew prevalence estimates. Nonetheless, the observed global disparities in the burden of OA may be attributed to a complex interplay of genetic, metabolic and behavioural factors, including

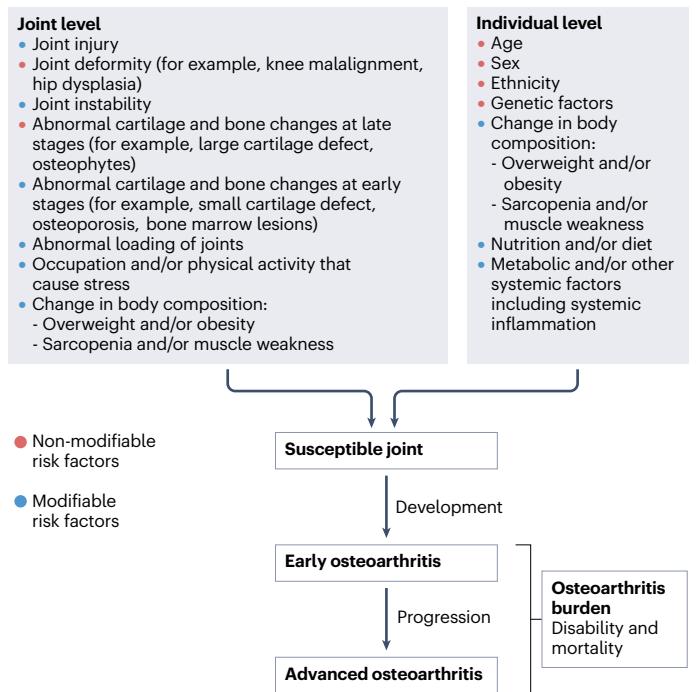


Fig. 3 | Summary of osteoarthritis risk factors. This figure outlines the hierarchical relationship between individual-level (influenced by genetic, systemic and lifestyle factors) and joint-level (specific to joint anatomy and function) risk factors that contribute to the susceptibility, progression and burden of osteoarthritis. Modifiable risk factors (blue) and non-modifiable risk factors (red) are also displayed.

variations in occupational activities, body mass index (BMI) levels, and physical activity like kneeling or squatting.

Looking forward, projections indicate a dramatic increase in OA cases by 2050, with an estimated increase for knee OA (74.9%), hand OA (48.6%), hip OA (78.6%) and other types of OA such as shoulder OA and foot and ankle OA (95.1%). This forecasted rise is owing to factors such as population growth and ageing. By 2050, the global number of people living with knee OA is expected to reach 642 million, followed by 279 million with hand OA, 62.6 million with hip OA and 118 million with other types of OA²⁰. These alarming trends emphasize the urgent need for robust public health strategies and interventions to manage the increasing global burden of OA.

Risk factors – individual level and joint level

As the most common form of arthritis, OA occurrence rises significantly with age owing to cumulative exposure to various risk factors and age-related changes in joint structures, although ageing and OA are independent processes²³. The OA risk escalates further under the impact of overweight and obesity, which intensify the stress on weight-bearing joints and potentially trigger systemic inflammation that affects all joints^{24,25}. Besides increasing adiposity, changes in body composition, such as the loss of skeletal muscle mass and function, known as sarcopenia, are also recognized as contributing risk factors to OA^{26,27}. OA occurrence is influenced by many modifiable and non-modifiable risk factors that affect individuals and specific joints in various ways. Individual-level and joint-level risk factors for OA have been identified (Fig. 3).

Sex also plays a crucial role, with women being more susceptible, showing sex-specific differences in both the presence and relative risk of several risk factors, including obesity²⁸. Occupational and lifestyle factors add another layer of complexity; repetitive and heavy physical activities exacerbate the risk, making OA more prevalent among those in physically demanding jobs²⁹.

At the joint level, previous joint injuries, such as anterior cruciate ligament (ACL) rupture, significantly increase OA risk by altering joint mechanics and loading, often leading to uneven stress across the joint surfaces³⁰. Joint deformity, such as knee malalignment or severe knee laxity, or abnormal displacement or rotation of the tibia with respect to the femur contribute similarly by disturbing normal joint function and accelerating OA development^{31,32}. Femoroacetabular impingement may predispose those affected to developing future hip OA³³. In 2015, a systematic review showed that individuals with overweight have an odds ratio (OR) of 1.98 (95% CI 1.57–2.20) for developing knee OA-related pain, while obesity is associated with a higher OR of 2.66 (95% CI 2.15–3.28). Previous knee injuries presented an even greater risk, with an OR of 2.83 (95% CI 1.91–4.19). The population-attributable fractions indicated that 24.6% of new knee pain cases could be attributed to having overweight or obesity and 5.1% to previous knee injuries³⁴. In addition, emerging evidence highlights the metabolic dimensions of OA, suggesting that conditions like diabetes and hyperlipidaemia, which affect systemic inflammation and metabolic health, may predispose individuals to OA or exacerbate its progression³⁵. These insights into individual-level and joint-level risk factors underscore the multifaceted nature of OA risk, which necessitates broad and inclusive prevention and management approaches, aiming to address the diverse factors contributing to OA disease.

Genetic risk factors. Genetic factors significantly influence the risk and progression of OA, with variations in genetic risk apparent across different joint sites³⁶. Genome-wide association studies have identified over 120 genetic loci associated with various OA phenotypes, highlighting the complex genetic underpinnings of this disease³⁷. Several detected genes are implicated in key structural and inflammatory pathways. For instance, alterations in *COLGALT2* and *TSEN15*, involved in collagen biosynthesis, may affect cartilage integrity, potentially leading to OA³⁸. The *KANSL1* gene is linked to developmental dysplasia of the hip and takes part in mechanisms that might predispose individuals to hip OA through an altered cartilage matrix³⁹. *CHRFAM7A* gene expression was found to exacerbate OA-associated inflammation, highlighting its potential as a target for therapies aimed at reducing inflammation in patients with OA⁴⁰. Furthermore, the genetic architecture of OA includes genes involved in pain perception, another important aspect of the disease. Variants in genes such as *CASPS*, *RASGEF1A* and *CYP4B1* have been linked to severe chronic pain following joint arthroplasty, indicating a genetic component to pain sensitivity and chronic pain management in patients with OA⁴¹.

Understanding these genetic factors provides valuable insights into the molecular pathways involved in OA pathophysiology and may guide the development of targeted therapies aimed at modifying disease risk and progression based on individual genetic profiles³⁷.

Comorbidities and mortality

In addition to the impact of OA progression on disability and societal costs, OA itself increases the risk of developing multiple other chronic conditions, creating an overall greater burden of disease. In a large primary care electronic health record data base study from the

Netherlands, investigators demonstrated that individuals diagnosed with knee or hip OA had an increased risk of being subsequently diagnosed with ~30 different comorbidities, including depression, diabetes and coronary artery disease⁴². In a similar study conducted in Sweden, an increased risk of many of the same comorbidities was noted, including again depression and cardiovascular disease as well as back pain and osteoporosis⁴³. A systematic literature review and meta-analysis analysing 42 studies with data from 16 countries reported that two-thirds of individuals with OA had a comorbidity⁴⁴. People with OA had a ~20% higher prevalence of having any comorbidity compared with those who did not have OA, and one-quarter of people with OA had three or more comorbidities, highlighting the burden of multimorbidity in OA. The most prevalent comorbidities were hypertension and dyslipidaemia, and the prevalence of cardiovascular disease was 56% higher in those with OA than in those without. Of concern, upper gastrointestinal disorders, and peptic ulcer disease in particular, had a greater than twofold higher prevalence among people with OA than those without, likely reflecting the adverse effects of non-steroidal anti-inflammatory drug (NSAID) use for symptomatic management of OA⁴⁵.

Additionally, OA has increasingly been recognized to have an elevated mortality risk. In 2016, a white paper produced by OARSI including a systematic literature review studying 20 years of data (1995–2015) reported an overall higher risk of mortality⁴⁶. The pooled risk, adjusted for age, sex and race, was 23% higher for those with symptomatic radiographic knee OA than for those without (95% CI 1.07–1.42) and was 20% higher for those with hip pain (with or without radiographic features) (95% CI 1.04–1.37). Not surprisingly, an even larger contributor to this mortality risk is the high cardiovascular comorbidity and walking disability burden among people with OA⁴⁷. In 2019, a population-based cohort from the UK reported that some of the excess mortality risk is also mediated through depression, anxiety and unrefreshed sleep, often associated with OA⁴⁸. Thus, addressing common comorbidities in OA is an important management focus to help reduce mortality risk.

Mechanisms/pathophysiology

A cascade of events is initiated in the joint structures during OA onset and progression, manifesting as systemic inflammation, fibrosis, extracellular matrix (ECM) degradation, neovascularization and neural sensitization³. Notably, the pathogenic changes occurring within each tissue type do not occur in a strict temporal sequence but rather as a complex, interrelated process. They exert influences upon adjacent tissues, creating a pathologically interconnected network that drives OA progression. This intricate interplay of pathological events and the diversity of underlying mechanisms underscore the complexity of OA as a disease entity. Understanding these multifaceted interactions is essential for developing targeted therapeutic strategies. Additionally, recognizing the heterogeneity inherent in OA reflected in distinct clinical phenotypes and molecular endotypes is crucial owing to its multifactorial nature.

Phenotypes and endotypes

The medical term 'phenotype' refers to any observable characteristic or manifestation of a disease, including morphological, developmental, biochemical or physiological traits as well as behavioural features, while the term 'endotype' describes the underlying molecular pathological mechanisms, identified and defined by specific cells or biomarker molecules found in blood or other bodily fluids to explain the detected characteristics of a phenotype.

The identification of OA phenotypes and endotypes remains a topic without a consensus; however, several proposals have been formulated⁴⁹ (Fig. 4). In 2018, six distinct knee OA phenotypes have been identified: inflammatory, bone and cartilage metabolism, minimal joint disease, chronic pain, metabolic syndrome, and mechanical overload⁵⁰. Another group proposed slightly different phenotype descriptions based on the primary drivers of the disease: synovitis-driven inflammatory, metabolism-driven, age-driven, cartilage-driven, traumatic injury-driven and subchondral bone-driven types⁵¹. The Categorization of Osteoarthritis Checklist (COACH) project categorizes OA into load-driven,

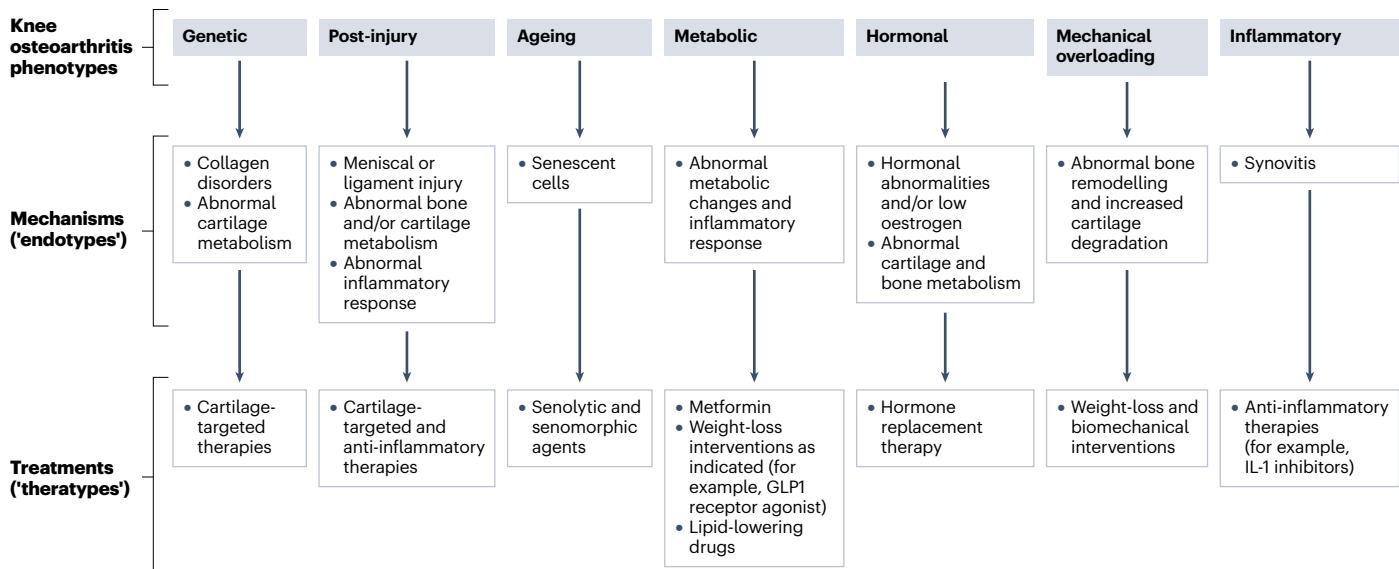


Fig. 4 | Knee osteoarthritis phenotypes. Example of how the concept of phenotyping/endotyping/theratyping can be used to maximize treatment success in knee osteoarthritis, noting that phenotypes may not be exclusive,

so different treatment types (or combinations of treatments) may be suitable to the same patient. Reprinted from ref. 49, CC BY 4.0.

structural-driven, inflammatory-driven, metabolic-driven, systemic factor-driven and mixed types⁵². Another unsupervised machine learning method approach to identify OA endotypes in the APPROACH cohort of patients with knee OA (297 patients) by clustering 16 biochemical markers associated with various joint tissue processes (for example, degradation, formation or inflammation) measured at baseline⁵³ revealed three distinct OA endotypes: (1) low tissue turnover (the highest proportion of non-progressors); (2) structural damage (linked to longitudinal structural progression); and (3) systemic inflammation (linked to sustained or progressive pain). It is important to note that the phenotypic classification proposed is not mutually exclusive, and more than one phenotype and ensuing endotype can exist within an individual.

Over the past decades, the heterogeneity in OA phenotypes and endotypes has been a major factor underlying the failure of numerous clinical trials aimed at assessing disease-modifying OA drugs (DMOADs). Significant differences in clinical presentations, imaging features and biomarkers among patients with OA hinder clinical trials targeting specific therapeutic interventions to achieve consistent efficacy. In addition, different OA phenotypes exhibit significant variability in response to the same treatment regimen and should therefore be treated differently. For instance, clinical trials aimed at improving pain or inflammatory responses require a patient cohort with prominent synovitis, while trials focusing on improving metabolism or weight need to carefully select patients with OA and high BMI. These instances emphasize that existing in-depth research methodologies often overlook the complexity of the disease, leading to high failure rates in clinical trials. Accurate OA phenotype and endotype definitions hold significant value in scientific research, clinical diagnosis and treatment. Most importantly, they assist in the more precise selection of patient populations for OA-related clinical trials, thereby shortening research timelines, reducing sample sizes and ultimately developing more effective therapeutic interventions.

Pathological changes in joint tissues

While OA can affect any joint, the mechanisms described herein predominantly reflect findings from studies on the knee and hip joints. These are the most affected and studied joints, providing the bulk of our current OA pathophysiology understanding. Insights into OA development and progression stem from both animal models and human tissue studies, both contributing consistent information to the overall picture. Animal models allow for the controlled investigation of disease processes and interventions, while human studies provide crucial real-world data, highlighting the variability and complexity of OA in clinical settings. OA is a joint-wide disease affecting and involving molecular and mechanical crosstalk between multiple tissues in addition to systemic processes and pathways⁵⁴. Here, we explore the pathological events within various joint structures (Fig. 5) and have to stress that it is important to consider the variability in how these processes manifest across different joints and individuals, particularly as the disease progresses.

Cartilage. Chondrocytes are located within cartilage lacunae, encompassed by a rich avascular ECM. In OA cartilage, an inflammation-amplifying subpopulation of chondrocytes expressing IL-1R1 (CD121A) and TNFR2 (CD120B) is markedly expanded⁵⁵. The subpopulation of senescent chondrocytes expressing senescence marker P16^{INK4A} also increases⁵⁶. Notably, the presence of pre-fibrocartilage chondrocytes stratifies OA into inflammatory and non-inflammatory subtypes⁵⁷. Changes in the types and numbers of chondrocyte subpopulations

induce a substantial reduction in hyaluronic acid, proteoglycan 4 (PRG4) and type II collagen in osteoarthritic cartilage due to chronic wear and imbalance between anabolic and catabolic (characterized by expression of collagenases and aggrecanases such as matrix metalloproteinase 13 and ADAMTS5) processes within the tissue⁵⁸. The diminished presence of these critical components results in compromised mechanical properties and an impaired ability to bear physiological loads. Morphologically, osteoarthritic cartilage also undergoes pronounced structural changes. The typically organized architecture of collagen matrix, characterized by arching fibrils, becomes disorganized⁵⁹. Such disordered fibrillary distribution weakens the structural integrity of the cartilage, leading to its mechanical degradation. The cumulative effect of these compositional and morphological changes further causes reduced cartilage stiffness and increased mechanical strain in osteoarthritic cartilage. Cartilage fibrosis occurs during the repair process of damaged hyaline cartilage, where proliferating chondrocytes transform into fibroblast-like phenotypes⁶⁰. This transformation involves the synthesis of type I collagen, which induces the degradation and dedifferentiation of the surrounding hyaline cartilage, ultimately forming a thick layer of fibrocartilage-like tissue^{61,62}. Fibrotic cartilage loses the properties of hyaline cartilage such as water retention and wear resistance.

Chondrocytes perceive the surrounding physical relief through a series of mechanosensitive receptors and channel receptors (reviewed in ref. 63). These receptors and channels activate a network of diverse downstream signalling pathways to regulate key cellular processes involved in the pathogenesis of OA, including inflammatory responses, the anabolic–catabolic axis and cell apoptosis. Identifying the spatiotemporal patterns of the intra-articular mechanical microenvironment will assist in designing mechano-responsive biomaterials and enable early intervention in OA pathological changes.

Subchondral bone. There are distinct pathological changes in the subchondral bone across the different OA stages. During early-stage OA, increased osteoclastic activity and trabecular bone loss are observed in subchondral bone, indicating a thinner and more porous subchondral bone plate^{64–66}. These early alterations can diminish the shock-absorbing capacity of the subchondral bone, subsequently accelerating the overlying cartilage loss. Bone marrow lesions, one of the early signs of OA generally detected by MRI, manifest as disrupted trabecular connectivity, microfractures of trabeculae, increased porosity of the subchondral bone plate, reduced trabecular thickness, decreased ratio of subchondral bone volume to total bone volume and altered subchondral bone absorption^{67,68}. Notably, bone marrow lesions usually appear before the loss of cartilage.

Late-stage OA is characterized by subchondral bone sclerosis and osteophyte formation. Increased bone mass in these lesions does not suggest improved bone quality⁶⁹. Instead, the high bone turnover rate and the decreased calcium-to-collagen ratio contribute to poor bone mineralization, which indicates reduced elastic modulus of the bone tissue and lesser stiffness. As such, the ability of subchondral bone to effectively absorb and distribute mechanical loads is damaged, making it more susceptible to deformation under stress^{70,71}. This deterioration in mechanical robustness is crucial for OA progression, pointing to the necessity of addressing both bone and cartilage health in OA treatment.

Synovium and infrapatellar fat pad. The joint cavity is lined by synovium, which is responsible for the production of synovial fluid harbouring nutrients and lubricating agents such as lubricin and

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hyaluronic acid (indispensable for low friction properties)⁷². Adjacent to the sublining layer is the infrapatellar fat pad (IPFP), which is increasingly considered part of a unified anatomo-functional unit with the synovium⁷³. While adipocytes exist within the synovium, collagen fibres and interspersed synovium are evident in the IPFP region. Single-cell RNA sequencing studies revealed that the synovium and IPFP share common mesenchymal progenitor cells with dipeptidyl peptidase 4

(DPP4) as a surface marker, both in human and murine tissues^{74,75}. This integrated perspective of the IPFP and synovium emphasizes their combined contributions to joint resilience and function, reflecting their significance in both healthy joint maintenance and the pathophysiology of joint diseases.

Tissue inflammation, fibrosis and vascularization are hallmark pathological alterations in OA synovium and IPFP. Synovial

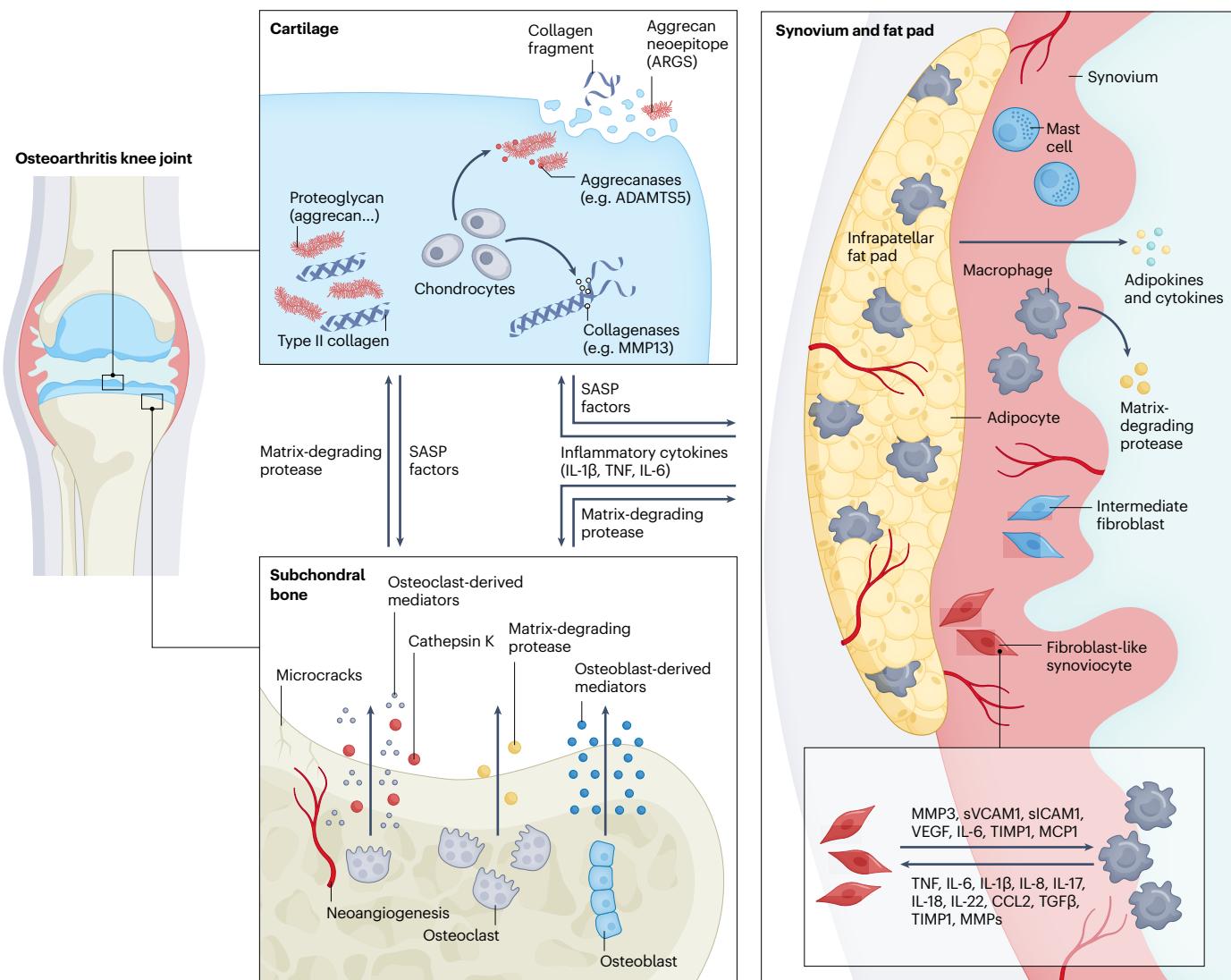


Fig. 5 | Pathological changes in knee joint tissue. Knee osteoarthritis is one of the most common joint diseases, characterized by pathological changes that involve the degradation of articular cartilage, inflammation and fibrosis of the synovium and infrapatellar fat pad, and remodelling of the subchondral bone. Cartilage degradation is driven by the excessive activity of matrix metalloproteinases (MMPs) and ADAMTS enzymes, leading to the breakdown of collagen and proteoglycans, resulting in cartilage becoming thinner and cracked, compromising its cushioning function, and causing joint pain and stiffness. Meanwhile, synovial tissue shows chronic inflammation, including congestion, synovial cell hyperplasia and inflammatory cell infiltration, increasing inflammatory factors in the synovial fluid and further damaging the cartilage. The infrapatellar fat pad is also affected, with fibrosis potentially altering mechanical properties around the joint, affecting movement. The subchondral bone undergoes significant structural changes such

as sclerosis and abnormal remodelling, which can lead to osteophyte formation, altering joint mechanics and increasing cartilage load. The sclerosis changes stress distribution within the joint, exacerbating cartilage damage. These pathological processes are interconnected, forming a complex network where inflammatory factors, such as IL-1 β , IL-6 and TNF, further promote cartilage degradation and synovial inflammation. Mechanical stress signals activate chondrocytes and bone cells, accelerating lesion progression. Senescence-associated secretory phenotype (SASP) factors from chondrocytes or matrix-degrading enzymes secreted by osteoclasts and synovium/fat pad cells interact to exacerbate tissue damage, highlighting the importance of understanding these cellular and molecular interactions for effective osteoarthritis treatment. ARGS, aggrecan generated aggrecan amino acids alanine, arginine, glycine, serine. Adapted from ref. 261, Springer Nature Limited.

inflammation, or synovitis, is characterized by the proliferation of fibroblast-like synoviocytes and the recruitment of macrophages, which induce hyperplasia of the synovial lining layer⁷². Activated fibroblast-like synoviocytes and macrophages secrete matrix metalloproteinases related to ECM degradation, causing significant alterations in synovial fluid composition⁷⁶. Concurrently, pro-inflammatory cytokines, including IL-1 β , TNF and IL-6, are released by pro-inflammatory macrophages undergoing pyroptosis, necrosis or senescence, further promoting cartilage degradation⁷⁷. Vascularization is marked by the formation of new blood vessels within the synovium and IPFP. This neovascularization not only facilitates the influx of immune cells, which exacerbates inflammation, but also contributes to the supply of nutrients that support the pathological changes in affected tissues⁷⁸.

Meniscus, ligaments and peri-articular muscles. The intricate relationship between the meniscus and OA lies in their potential bidirectional causality. Pathological alterations in the meniscus, including tears, extrusion and decreased vascularization, can promote the degradation of articular cartilage^{79,80}. Conversely, OA progression can induce or exacerbate meniscal degradation⁸¹. Similar phenomena occur in intra-articular ligaments (ACL and posterior cruciate ligament). Ligament laxity or rupture leads to joint instability and accelerates OA pathology, which in turn triggers ligament damage⁸². The peri-articular muscles are involved in maintaining joint stability and function. Vastus medialis fat infiltration, reduced muscle cross-sectional area and decreased muscle strength are observed in the muscles around the knee joint of patients with OA^{83,84}. Additionally, ultrasound can detect changes in muscle echogenicity (the brightness of muscle tissue on an ultrasound image, indicating its ability to reflect ultrasound waves), which may correspond to pathological alterations such as oedema or fibrosis. Unlike muscle strength, muscle quality, including echo intensity and shear wave velocity, may affect knee OA pain, suggesting its value as a target for OA pain treatment⁸⁵.

OA-associated pain

In OA, pain was long considered a symptom disconnected from joint damage. Certainly, there is a well-documented discordance between reported pain and radiographic findings⁸⁶, especially in knee OA. However, individual-specific factors may drive this discordance, and when between-person confounding is minimized, radiographic OA and individual radiographic features are, in fact, strongly associated with knee pain⁸⁷. MRI – which images soft tissues – has revealed synovitis and subchondral bone marrow lesions correlating with OA pain⁸⁸. Synovitis and inflammation are strongly correlated with pain, and anti-inflammatory drugs, such as NSAIDs and glucocorticoids, have analgesic effects in OA^{89,90}.

Pain starts with nociception, the detection of potentially noxious stimuli in peripheral tissues by specialized sensory neurons called nociceptors. These afferents transmit signals from peripheral tissues, via their cell bodies in the dorsal root ganglia, into the central nervous system (Fig. 6a). Information arriving in the dorsal horn of the spinal cord is transmitted to higher regions of the neuraxis, and ultimately processed by the brain as pain⁹¹. Anxiety, depression, fatigue, sleep and catastrophizing can modulate these pathways and contribute to the pain experience⁹². Importantly, arthroplasty results in pain relief in most patients with knee OA, underscoring the peripheral drive of pain in OA. Hence, a precise description of the properties of the neuronal pathways that mediate nociceptive signalling is essential for

understanding OA joint pain. These pathways undergo considerable plasticity as joint damage progresses, with changes in the structural and physiological properties of neurons in pain pathways. Two fundamental processes operate in an OA joint: peripheral sensitization and anatomical neuroplasticity.

Peripheral sensitization. Nociceptors that innervate an inflamed or injured tissue become hyperexcitable, meaning that the threshold for activation (such as firing of action potentials) is lowered so that they respond to non-noxious stimuli. This clinically manifests as allodynia (when innocuous stimuli are perceived as painful) and hyperalgesia (when the response to a painful stimulus is exaggerated). Patients with OA are sensitized to mechanical stimuli as detected by quantitative sensory testing (QST)⁹³.

Many mediators present in OA joints can contribute to sensitization, including cytokines, chemokines and disease-associated molecular patterns⁹⁴. Nociceptors express receptors for these mediators and, in laboratory animals, intra-articular injection of IL-1 β , IL-17, TNF, IL-6 and CCL2 results in hypersensitivity to mechanical stimuli. Of particular interest in OA, a small aggrecan-derived peptide, generated through enzymatic cleavage when ADAMTS4/5 and MMPs cleave the aggrecan core protein, elicits knee hyperalgesia upon intra-articular administration⁹⁵. This underscores how mediators released by cartilage, which has no nervous tissue, can contribute to sensitization and pain. In this regard, the neurotrophin nerve growth factor (NGF) is of major interest since its expression is increased in OA cartilage and other joint tissues⁹⁶. NGF sensitizes nociceptors through binding its high-affinity receptor TrkA, and NGF–TrkA signalling also increases the expression of neuropeptides and other pain-promoting molecules^{97,98} (Fig. 6b).

The critical role of NGF in OA pain was clinically demonstrated in successful trials that administered neutralizing antibodies against NGF (reviewed in ref. 99). In 2022, the development of anti-NGF came to a halt when the FDA did not approve this biological approach because of the poorly understood side effects in a small number of patients who developed rapidly progressive OA. Elucidating mechanisms of this side effect will be of critical importance since it may shed light on the relationship between pain and joint integrity.

Anatomical neuroplasticity. To understand the contribution of peripheral nociceptors to pain sensation, it is paramount to precisely describe their anatomical distribution in the joint. Joint tissues, including subchondral bone, synovium, menisci, tendons, ligaments and periosteum, are richly innervated by sensory neurons (predominantly nociceptors)^{100,101}. During progressive OA, innervation patterns change. In human OA knees, osteochondral channels that breach the tidemark between subchondral bone and articular cartilage contain blood vessels and neurons^{102,103}, and the presence of CGRP-immunoreactive nociceptors in these channels is associated with pain¹⁰⁴. In experimental OA, progressive joint damage is associated with sprouting of nociceptors in subchondral bone and the medial synovium^{105,106} (Fig. 6c). In human OA knees, NGF can be detected in osteochondral channels and is associated with pain¹⁰⁷. Microarray analysis of bone marrow lesions has identified genes involved in neurogenesis as being upregulated¹⁰⁸. Therefore, factors mediating neuronal growth in OA joints should be explored as targets for joint pain.

To produce pain, sensory neurons and resident joint cells communicate. For example, fibroblast subsets from painful synovium sites in human knees can promote the growth and activity of neurons¹⁰⁹.

Immune cells, such as macrophages, in the arthritic joint can release mediators that sensitize nociceptors, and targeting STAT6-mediated synovial macrophage activation improves pain in experimental knee OA¹¹⁰. In human OA, a correlation exists between pain and joint macrophages. Activated macrophages were reported in 75% of symptomatic OA knees as well as in other painful joints such as ankles and great toes¹¹¹. Macrophages also infiltrate the dorsal root ganglia (reviewed in ref. 112), and depletion of macrophages in the nervous system alleviates pain in experimental models¹¹³.

Central sensitization is a feature of all chronic pain syndromes and occurs at multiple levels of the central nervous system⁹¹. Extensive evidence gathered by QST and functional brain MRI suggests that central sensitization contributes to OA pain^{114,115}. In many patients, evidence of central sensitization subsides in response to treatments that dampen peripheral drivers of OA pain such as total knee replacement (TKR). Furthermore, pre-treatment QST can sometimes identify persons who are less likely to experience pain relief from surgical and non-surgical treatments for knee OA⁹³. The precise relationships

between sensitization, pain, joint damage and TKR need further elucidation.

Diagnosis, screening and prevention

Clinical presentation, symptoms and signs

The assessment of OA usually focuses on symptoms obtained through taking a history (such as pain, stiffness, functional impairment) followed by an assessment of signs (such as crepitus on movement, joint line tenderness and restricted range of motion) that are typically assessed during a physical examination. Knee pain on activity, especially on pivoting and twisting and perceived knee joint stiffness are among the first symptoms of knee OA. Of note, these indicators can occur several years ahead of the objective radiographic signs of OA¹¹⁶. The stiffness of the joint, also called morning stiffness, appears after inactivity. Morning stiffness in OA is often of shorter duration than in rheumatoid arthritis (usually less than 30 min in knee OA versus longer than 30 min in rheumatoid arthritis, and less than 60 min in hip OA) and improves after moving the joint^{117,118}.

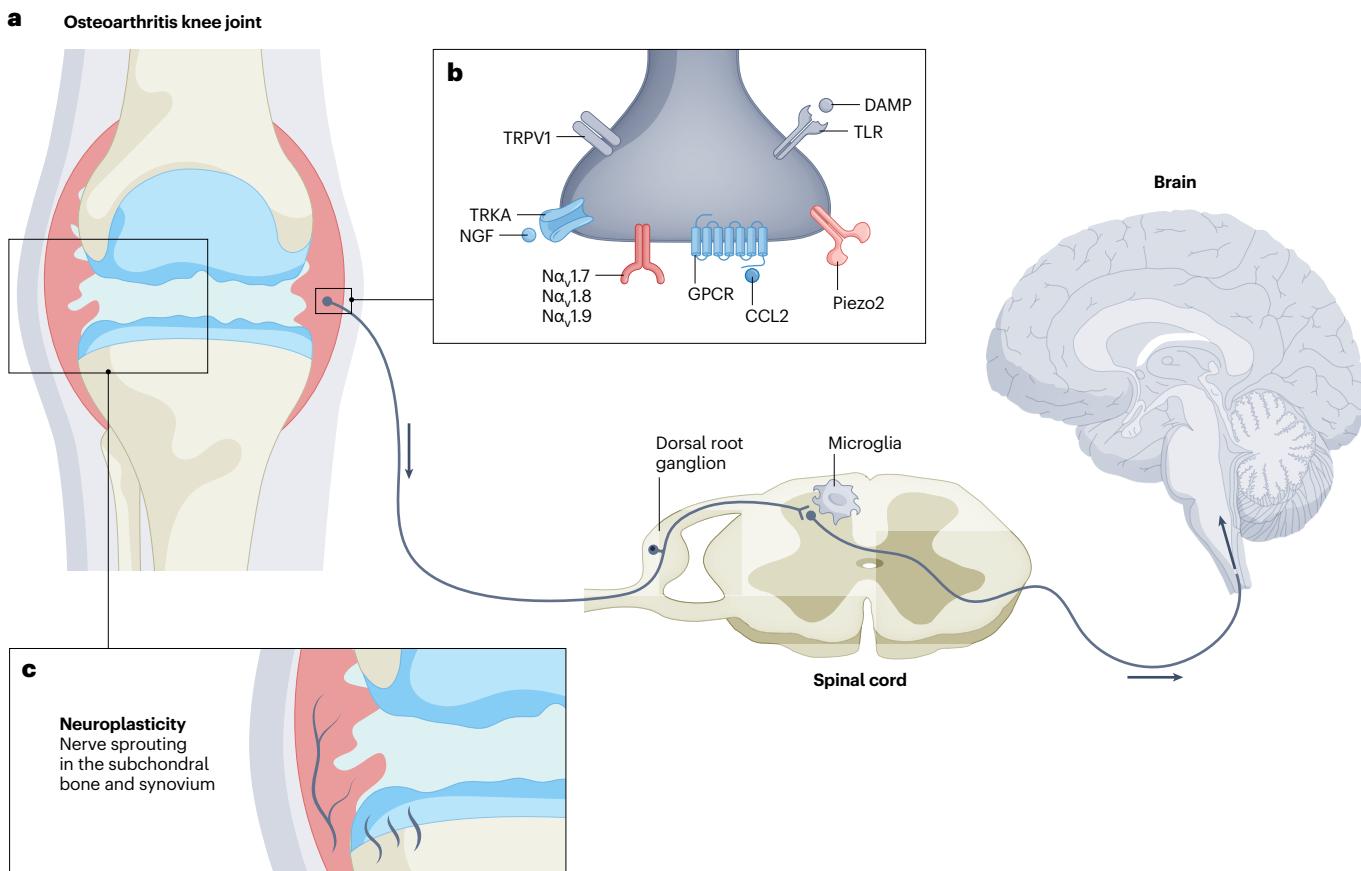


Fig. 6 | Neuroanatomy of the pain pathway in osteoarthritis. **a**, Overview of the peripheral pain pathway in joint pain. Noxious stimuli activate the peripheral terminals of nociceptors that innervate joint tissues. Depolarization of nerve terminals initiates the firing of action potentials that invade the dorsal root ganglia, where the cell bodies reside. This requires the activation of voltage-gated sodium channels Na_v1.7, Na_v1.8 and Na_v1.9. Signals are transmitted to the dorsal horn of the spinal cord, where nociceptors synapse with second-order neurons – either interneurons (not shown) or projection neurons that cross to the contralateral side and carry the signal up the spinal cord. From there, the signals

are propagated to higher regions of the central nervous system and different areas of the brain, where they are perceived as pain. **b**, Peripheral terminals of nociceptors express voltage-gated sodium channels and ion channels, such as TRPV1, or mechanosensitive ion channels such as Piezo2. They also express receptors for inflammatory mediators released by degrading and inflamed joint tissues, such as nerve growth factor (NGF), CCL2 or disease-associated molecular patterns (DAMPs). **c**, Anatomical neuroplasticity occurs as part of osteoarthritis pathology, including neo-innervation of the synovium and sprouting of nociceptors in the subchondral bone, which may breach the tidemark.

OA is often accompanied by a loss of range of motion, which, on top of the pain, contributes to the functional limitations in everyday life. Patients also reported a lack of confidence in their joint and a feeling of buckling or giving-way while walking¹¹⁹.

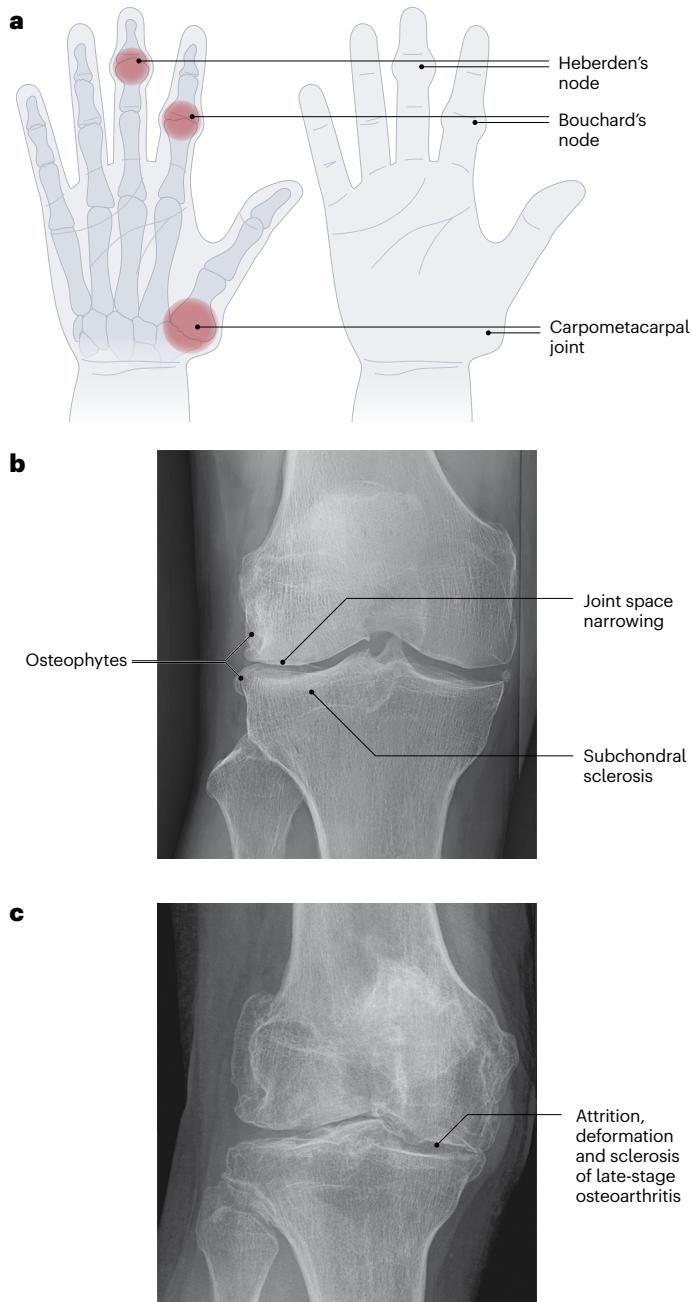


Fig. 7 | Imaging assistance when clinical findings of symptoms and signs suggest an alternative diagnosis. A diagnosis of osteoarthritis can typically be made based on classic clinical symptoms that may display externally visible features such as Heberden's and Bouchard's nodes (part a), followed by physical examination. In an atypical case, where other differential diagnoses are likely, the X-ray may show traditional structural features of osteoarthritis joint space narrowing, osteophytes and subchondral bone sclerosis (part b). Late-stage disease may show attrition and deformation of the joint on X-ray imaging (part c).

Although OA pain can be absent for longer periods in the initial years, it might become more chronic, sensitized and disabling over time¹²⁰. Sleep disorders, fatigue and depression can contribute to further worsening of these conditions¹²¹. Nocturnal pain has been reported by most patients with hip and knee OA and appears to be independent of the structural severity of the disease^{122,123}. Intense and unpredictable pain, and the impact of pain on mobility, mood and sleep, are the most distressing pain features for patients living with OA¹²⁴.

During physical examination, some signs are very specific for OA, such as Heberden's and Bouchard's nodes, observable as bony swellings at finger joints, in the distal interphalangeal joint and proximal interphalangeal joint, respectively¹²⁵ (Fig. 7a). If palpable, like in the knee, joint margins can be painful under palpation. Crepitus, a grating noise that accompanies flexing a joint, was reported when the knee joint is passively moved from flexion into extension and vice versa, and a wider joint called 'bony enlargement' can be observed in some patients with OA¹²⁶.

Physical exam can also reveal typical atrophic muscles, such as a smaller quadriceps muscle in knee OA, the thenar muscle in thumb-base OA and the hip abductor muscle in hip OA^{127–129}, resulting in loss of range of motion in specific directions^{117,118}. Synovial joint effusion can occur in patients with OA¹³⁰. The degree of synovitis will differ between patients and can fluctuate over time. In patients with OA of the lower extremities, the pain and restricted range of motion are reflected in a walking pattern with lower speed and a shorter step and stride length¹³¹.

There is a broad consensus that the diagnosis can be made based on the clinical symptoms and signs but medical imaging can be considered in case of atypical presentation or of strong suspicion of an alternative diagnosis such as pseudogout, tendinopathy or inflammatory arthritis³. X-ray is the usual and recommended imaging modality, aiding in the assessment of traditional structural features of OA, such as joint space narrowing (indirect visualization of cartilage loss) and osteophytes (bone spurs at the joint margins), subchondral bone sclerosis and, at later stages, cysts and joint deformation (Fig. 7b,c). Where there is ongoing diagnostic uncertainty, second-level investigations that are more suitable for the detailed assessment of soft tissues (MRI and ultrasonography) or bone (CT) may be considered¹³².

Diagnostic criteria

Several decades ago, The American College of Rheumatology (ACR) defined classification criteria for OA of the knee, hip and hand^{117,118,133}. In 2023, the European League Against Rheumatism (EULAR) presented, for the first time, classification criteria that specify the different types of hand OA¹³⁴. The development of these classification criteria moved through two phases. First, they identified hand OA features by comparing patients who received a physician-based hand OA diagnosis with controls with hand complaints resulting from other inflammatory or non-inflammatory conditions¹³⁵. Second, they identified features that could help differentiate overall hand OA from interphalangeal OA and thumb-base OA¹³⁶. The criteria places a heavy emphasis on plain radiographic characteristics, ensuring that these are people with established OA and not early-stage OA. These criteria still need to be validated in further large cohort studies.

Of note, the classification criteria are designed to classify patients for research purposes. High specificity is preferred for such research classification criteria to ensure that it is reasonably certain that the patients have the disease. However, these criteria have also often been used as diagnostic criteria. The EULAR diagnostic criteria for knee OA use a different analytical approach incorporating

both research evidence and expert consensus as well as validation in two distinct populations to increase confidence in their clinical application¹³⁷. Other published diagnostic criteria for OA of the knee and hip are the consensus-based National Institute for Health and Care Excellence (NICE) criteria from the UK¹³⁸. The different criteria for knee OA established by ACR, EULAR and NICE are compared in Table 1.

For many years, there has been a call for early-stage diagnostic or classification criteria to allow early-stage treatment before pain has become chronic and difficult to treat or structural changes adversely influence the biochemical and biomechanical joint environment. In 2021, the first early-stage diagnostic criteria for knee OA were published¹³⁹ and validated¹⁴⁰. According to history taking and physical examination data in these studies, pain at walking stairs, morning stiffness, joint line tenderness and effusion seemed to be the features that defined early-stage OA.

Differential diagnosis

Differential diagnosis includes other joint and bone diseases or disorders from the soft tissues. Other joint diseases include forms of arthritis such as rheumatoid arthritis, psoriatic arthritis and gout. Septic arthritis is rarer but should always be considered when there is a clear inflammation of the joint to prompt immediate treatment. For younger patients with knee pain (typically 12–20 years of age), patellofemoral pain syndrome could be considered⁸⁶. Peri-articular tendinitis and/or bursitis in hip, knee and thumb can be a differential diagnosis but they can also accompany OA and (partly) explain the complaints¹⁴¹. Bone diseases like (metastatic) bone tumours, stress fractures, tuberculosis and avascular necrosis in the hip can initially mimic OA complaints. In younger and physically active patients, femoroacetabular impingement or labral tear in the hip should be considered¹¹⁸. Such bone disease can be distinguished from OA via medical imaging¹³².

Joint pain can also be caused by radicular pain or pain referred from other areas. Pain felt in the anterior knee due to hip OA has been well established. Pain in the hip can also result from radicular pain from the lumbar spine.

Holistic evaluation

In addition to diagnosis, a holistic assessment should include the person diagnosed with the disease. The assessment includes an evaluation of how OA symptoms affect the patient's work, leisure and home situation, and whether they affect their mood and sleep. Relevant comorbidities also play an important role as do patient expectations and beliefs regarding the disease and certain treatments¹¹⁹. This information is required to educate the patient well, facilitate shared decision-making and develop a tailored evidence-based management plan.

Primary prevention of obesity and joint injury

Primary prevention programmes strive to manage risk factors, such as overweight, obesity and joint injury, prior to their manifestations. OA prevention programmes should be a major focus to oppose the predicted increase in OA prevalence, the burden of the disease, and the associated health-care and societal costs in the future^{20,142}. Prior to disease-modifying therapies being available for OA, there was an international call for OA prevention strategies addressing individual risk factors for incident disease and development^{1,143,144}.

The opportunities for implementing evidence-based strategies for the prevention of OA are numerous^{145–147}. Implementation of

Table 1 | Comparison of diagnostic criteria for knee osteoarthritis

	ACR criteria ^a	EULAR criteria	NICE criteria
Age	≥50	–	≥45 years
Symptoms			
Knee pain	Yes	Yes, persistent	Yes, activity related
No or short duration of morning stiffness (≤30 min)	Yes ^b	Yes	Yes
Functional limitation	–	Yes	–
Clinical signs			
Crepitus	Yes	Yes	–
Restricted range of motion	Yes ^b	Yes	–
Bony enlargement	Yes ^b	Yes	–
Joint margin tenderness	Yes ^b	–	–
No palpable warmth	Yes ^b	–	–

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; NICE, National Institute for Health and Care Excellence. ^aClinical classification criteria. ^bThree or more of these criteria should be present.

interventions linked to modifiable risk factors for OA, such as obesity and joint injury, should be of high priority^{145–148}.

Obesity onset prevention. Obesity is a well-known risk factor for knee OA, with weaker associations for hand and hip OA¹⁴⁹. Hence, primary prevention programmes as lifestyle interventions for those at risk of OA are highlighted and should be implemented¹⁵⁰. Primary prevention across the lifespan is needed, starting with children at risk¹⁵¹. Furthermore, many women-only interventions have been identified that also consider potential weight management challenges following pregnancy and menopause¹⁵¹. Primary prevention strategies have shown a potential to minimize adult-onset obesity¹⁵¹. However, adherence to interventions is poor and should be addressed by personalized and multi-modal interventions¹⁵².

Joint injury prevention programmes. A systematic review of high-quality studies showed a significant protective effect on injury rates and a 53% reduced injury rate in injury prevention programme outcomes¹⁴⁵. Another recent systematic review and meta-analysis confirmed that participation in injury prevention programmes is associated with decreased risk of ACL and lower extremity injury rates¹⁴⁸. In professional sports, pre-season and in-season programmes, including muscle strengthening, flexibility, balance and neuromuscular exercises, are key elements in reducing excessive knee loads¹⁵³, thereby reducing injury and post-traumatic OA (PTOA). In 2018, a study found that injury prevention programmes may be more effective if administered early in the athletes' career¹⁵⁴. In addition, younger athletes might be more likely to adopt new biomechanical movement patterns^{154,155}.

Translating knowledge into practice has taken a long time within this field¹⁴⁸. Today, the opportunities lie in implementing established evidence into practice, improving adherence to the programmes, educating coaches and increasing awareness for freely available prevention programmes¹⁵³. Educating athletes and coaches is still required to profit from the injury prevention programme benefits¹⁴⁸.

Secondary prevention of obesity and post-traumatic joint injury

For those with overweight or obesity and those with previous traumatic joint injuries (PTOA), notable opportunities for secondary prevention of OA exist^{144,147}. Early diagnosis of OA, when illness modification has the greatest potential for improving symptoms and function, is key¹⁵⁶.

Strategies for individuals with obesity. Weight loss in individuals with obesity or overweight and with OA has shown a significant reduction in joint pain and symptoms as well as less progression of cartilage degradation and meniscal lesions for 8 years compared to those with stable weight¹⁵⁷.

Both exercise and dietary interventions should be part of secondary prevention programmes for patients with knee OA to reduce weight as well as pain and symptoms (OA illness)^{158–160}. For those who underwent a programme with both diet and exercises, muscle mass was maintained, leading to improvements in pain and function and reduced compressive force on knee joint loads¹⁶⁰. Synthesized evidence from seven systematic reviews highlights recommendations for aerobic exercises at moderate intensity levels for weight loss¹⁴⁷. To preserve lean mass during weight loss, a moderate-to-high-intensity resistance programme, in addition to dietary interventions, is recommended¹⁵⁰. Sarcopenic obesity has been identified as another risk factor for knee OA^{161,162}; hence, muscle mass and muscle dysfunction should be an additional focus next to body fat mass composition in individuals with obesity¹⁶³.

A large observational cohort study found that adults receiving GLP1 receptor agonist treatment lost more weight and had fewer knee surgeries compared to those not receiving GLP1 receptor agonist treatment¹⁶⁴. In 2024, another, multicentre, placebo-controlled trial confirmed that the once-weekly application of the GLP1 receptor agonist semaglutide can reduce body weight and pain related to knee OA in individuals with obesity¹⁶⁵. These study outcomes indicate that pharmacological weight management is an important component of OA secondary prevention and management. However, further research is warranted to inspect sustaining the benefits obtained and their cost-effectiveness before widespread adoption can be advocated.

The main challenge of exercise and dietary interventions is the low adherence to interventions; personalized and multi-model strategies are therefore crucial¹⁶⁶. Practical, person-centred, implementable strategies to increase adherence to physical activity programmes for individuals with obesity and OA have been recommended and serve as opportunities for long-lasting effects of exercise adherence¹⁶⁶.

Post-traumatic osteoarthritis. More than 50% of those who undergo ACL reconstruction develop knee OA more than 10 years after injury¹⁶⁷, and there are no significant differences in OA between those who go through surgery after ACL injury compared to those who do not¹⁶⁸. Moreover, six risk factors for PTOA have been identified for those with ACL injury during adolescence and early adulthood: concomitant injuries (meniscus and cartilage injuries)^{144,169,170}, re-injuries after ACL injury¹⁷¹, impaired self-reported knee function 2 years postoperatively^{167,172}, long-lasting quadriceps dysfunctions^{146,173}, knee joint haemarthrosis and inflammation after joint injury¹⁷⁴. Quadriceps weakness and dysfunctions after ACL injury are common after traumatic knee injuries¹⁷³, associated with pain, and a recognized independent risk factor for the development of knee OA¹⁴⁶. Preventing re-injuries after primary ACL injury through re-establishing knee function prior to return to sport was found to be beneficial^{171,175}. Functional readiness

and normalizing quadriceps function, assessed by using return-to-sport criteria such as symmetrical quadriceps strength and hop test and delaying return to 9 months after ACL reconstruction, have been shown to reduce re-injury rates by 84%¹⁷¹.

Altering joint mechanics and loading after traumatic knee injuries leads to uneven stress across the joint surfaces, contributing to abnormal joint function. Persistent abnormal joint loading is an undisputed risk factor for developing OA^{63,176}, and the quadriceps muscle plays a central role in modulating loads across the knee joint^{177,178}. There is a considerable knowledge gap in understanding changes in mechanical joint stresses and persistent abnormal joint loading in individuals at high and low risk of developing PTOA.

Secondary prevention programmes focus on addressing the modifiable risk factors for PTOA by preventing re-injuries, normalizing joint loading, reducing persistent pain, normalizing quadriceps dysfunction¹⁷⁹ and preventing overweight or obesity¹⁷⁹. In 2024, Stop OsteoARthritis (SOAR) presented the outcomes of the first randomized controlled trials (RCTs) that addressed the risk factor of quadriceps strength deficits¹⁸⁰. However, the role of long-term quadriceps dysfunction on persistent abnormal joint loading remains to be revealed. Understanding the underlying mechanisms is crucial in the development of novel preventive interventions that aim to normalize joint loading in the long term^{146,171,173,175}.

Management

Current OA treatment approaches focus on symptomatic relief, ameliorating pain and improving joint function to master daily life activities¹⁸¹. Despite decades of extensive research efforts, there are no agents that have been proven to modify the course of OA disease, so-called DMOADs, that target both symptoms and structure.

Step-up symptomatic treatment includes non-pharmacological core approaches (education and self-management, lifestyle or behavioural changes, exercise therapy, weight loss (for individuals with overweight or obesity), and prescription of walking aids or braces) and application of pharmacological options (NSAIDs, topical or oral; and only if required (that is, after inadequate response to all other therapies), and intra-articular therapies such as steroids) to reduce pain and improve joint function¹⁸² (Fig. 8). Surgical interventions are usually reserved as a last resort for patients with OA with significant symptoms that interfere with their quality of life and who cannot be treated satisfactorily via non-surgical approaches^{138,181,183,184}.

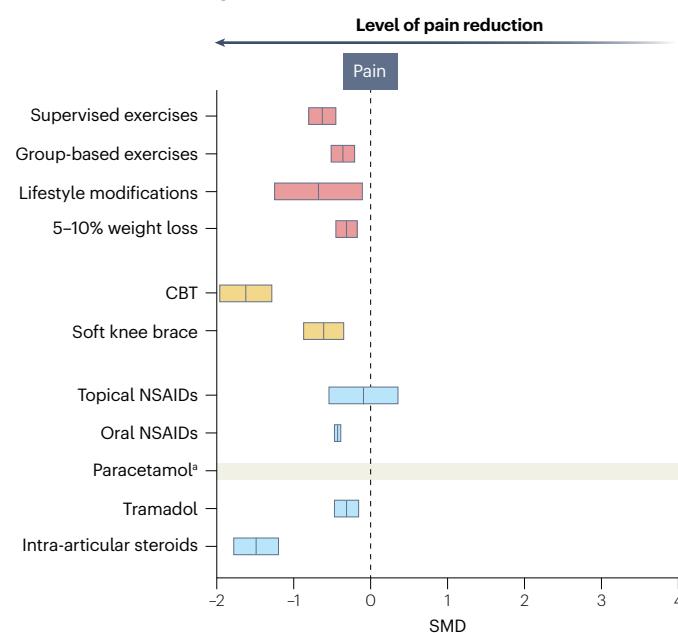
Insufficient uptake of guideline-recommended care

International consensus on first-line treatments for patients with knee and hip OA includes patient education, exercises and lifestyle changes^{185,186}. These first-line treatments have also shown to be cost-effective^{187–189}.

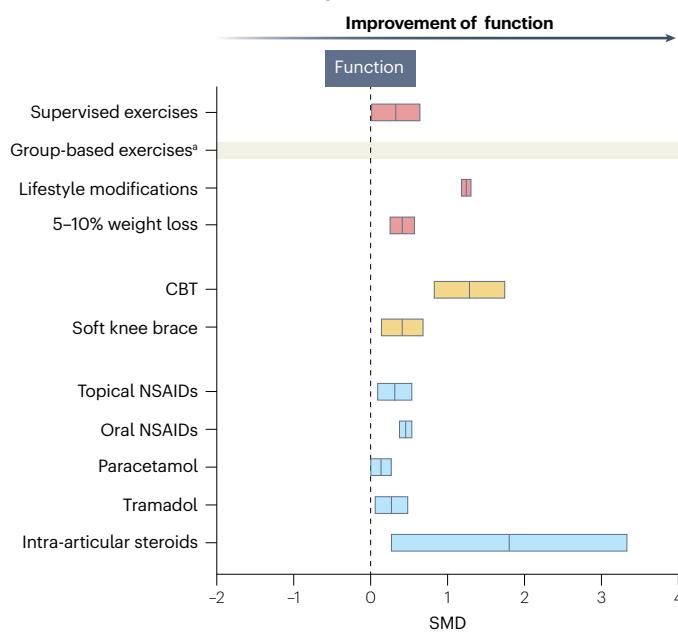
The consensus on first-line treatment is based on a high level of evidence¹⁹⁰, systematic reviews of clinical guidelines¹⁸⁵, and updated published recommendations from international organizations such as OARSI¹⁸¹ and EULAR¹⁸⁶. However, despite guideline concordance on available evidence and the predicted high future burden of the disease¹⁹¹, most people with OA do not receive treatment according to guidelines^{192–194}.

The uptake and fidelity of these guidelines among health-care professionals and patients are lacking^{195,196}. Only 6% of patients reported receiving a combination of all recommended treatments¹⁹⁷ and only one in five people used all of the recommended first-line treatments¹⁹². In another cohort, only 33% of patients with knee OA received the

a Treatment effect on pain reduction



b Treatment effect on function improvement



- First-line core treatments
- Second-line non-drug therapy
- Drug therapy
- No data

patient education component of the first-line treatment, 66% adhered to the exercise component, and 33% adhered to the weight reduction programme for those with overweight or obesity^{198,199}. Less than 40% of patients with OA in the community were offered education and/or self-management (35%, 95% CI 28–44%) or had received a recommendation for exercises (39%, 95% CI 29–50%)²⁰⁰. A Swedish ($n = 229$)²⁰¹ study

Fig. 8 | Effect sizes for core, adjunctive and pharmacological treatments for osteoarthritis.

This figure summarizes the core treatments (such as exercise, physical activity and weight management, as advocated by international clinical guidelines) as well as recommended adjunctive therapies and drug therapies for osteoarthritis and their individual effect on pain reduction (part a) and function improvement (part b). Negative standard mean difference (SMD) indicates beneficial effects in the intervention group compared with the control group.

^aData have not been provided in the original datasets. CBT, cognitive behavioural therapy; NSAID, non-steroidal anti-inflammatory drug. Adapted from ref. 182, Springer Nature Limited.

and a Canadian ($n = 1,273$)²⁰² study further reported that approximately 40% of patients with OA waitlisted for hip or knee arthroplasty had not previously received appropriate first-line core treatments.

Patient barriers to first-line treatment include non-covered costs, waiting times for clinic visits, a lack of services offered in the community, and patient beliefs and misinformation such as surgery being the only option and fear of exercise worsening pain and increasing disease progression²⁰³. Implementation is also hindered by service availability and reimbursement plans, resulting in a suboptimal OA treatment environment²⁰⁴. A systematic review conducted in 2023 examining exercise adherence in clinical trials for knee OA revealed a mean adherence rate of 67.9% across these trials (range 3.7–100%)²⁰⁵, with large heterogeneity in the methodology used; therefore, its impact on the clinical outcomes could not be determined. Another systematic review reported that booster sessions (90%) and telephone-linked communication (86%) resulted in higher exercise adherence by patients for more than 12 months²⁰⁶.

First-line treatment: educational, lifestyle and behavioural change programmes

Components of the education and behavioural change programmes generally consisted of information on disease education, self-care and pain coping strategies, exercise, nutrition, joint protection, shoe wear, assistive device use, and pain management²⁰⁷. Patient education alone (that is, any form of therapist-facilitated education, regardless of profession), compared to no education intervention, was associated with less knee pain and improved function²⁰⁸ although the difference may not be clinically important as an isolated intervention.

Of note, 87% of people with knee OA do not meet physical activity guidelines²⁰⁹, and the high prevalence of physical inactivity in people with OA has been associated with earlier mortality⁴⁸ while two-thirds of patients with hip and knee OA have comorbidities⁴⁴, including cardiovascular disease, type 2 diabetes, depression and Alzheimer disease.

Individually supervised exercises provided greater pain reduction than group-based exercises²¹⁰. However, there is currently no consensus on the best type of exercise for improving OA outcomes. At least 12 training sessions over 3 months with two sessions per week are recommended and essential to benefit from exercise therapy interventions²¹¹. Exercise programmes should be individualized and progressively overloaded with frequency, duration and intensity according to the patient's capability¹⁸⁵.

A minimum weight loss target of 5% of body weight is strongly recommended for people with hip and/or knee OA with either overweight ($BMI \geq 25 \text{ kg/m}^2$) or obesity ($BMI \geq 30 \text{ kg/m}^2$). In mild-to-moderate knee OA, 5–10% weight loss was associated with less pain and improved function²¹². A dose-response gradient of weight loss for

pain and function seems to be more obvious for body weight shifts of $\geq 10\%$ over a 3-year period and this linear effect is maintained up to 20% loss of baseline body weight²¹³. No clinically meaningful difference in the effectiveness of these combined core therapies (education, exercise, weight loss) was found with respect to sex, age, obesity, comorbidity, depression and imaging findings, implying that these core therapies should be offered to all patients with OA²¹⁴.

Second-line treatments

Adjunctive treatments are second-tier evidence-based options added to the core treatments, depending on the circumstances of individual patients. As a note, the number of adjunctive treatments included and the level of recommendations provided can differ among the international clinical guidelines²¹⁵, resulting from a lack of data on the effectiveness of the treatment or different interpretations of results from single studies or low-quality trials. Second-line treatments include cognitive behavioural therapy (CBT) and a knee brace.

CBT is an intervention where the thoughts, beliefs and feelings of the patient regarding OA-related illness and disability are addressed²¹⁶. In a 2021 meta-analysis in knee OA, face-to-face CBT interventions combined with exercises showed a reduction in the WOMAC pain subscale, a self-administered questionnaire that inquires on pain with specific activities with a possible score range of 0–20 for pain, while distance-delivered intervention combined with exercises also led to a reduction in the WOMAC pain subscale of a similar magnitude²¹⁶. However, the cost-effectiveness of such combined treatment is uncertain²¹⁷. A soft knee brace that augmented exercise therapy compared to no knee brace showed a reduction in pain and improved function²¹⁸.

Pharmacological interventions

Where first-line treatments have not adequately ameliorated symptoms, particularly to assist in managing flares, the use of pharmacological therapies primarily targeted to analgesia should be considered (Table 2). A 2020 network meta-analysis including 122 RCTs and 47,113 participants demonstrated that topical NSAID application was associated with moderate improvement in pain and function of a similar magnitude to oral NSAIDs and had a better safety profile and effect when compared to acetaminophen²¹⁹. In placebo-controlled RCTs in hip or knee OA, oral NSAIDs were associated with less pain and improved function at 2 weeks with attenuating effects over 26 weeks²²⁰. NSAID-associated risk mitigation strategies, such as regular monitoring for adverse reactions, minimizing dose and keeping treatment duration brief, should be followed as advocated in the ACR guidelines¹⁸³.

According to the 2019 ACR and 2022 NICE guidelines, intra-articular administration of steroids was recommended for short-term efficacy (moderate quality evidence) as second-line treatment, whereas intra-articular hyaluronic acid injection has not been recommended due to low-quality evidence¹⁸³. A 2021 meta-analysis demonstrated that intra-articular steroids resulted in less pain and caused functional improvement for up to 6 weeks compared with intra-articular saline; here, no serious adverse events were reported²²¹. Of note, concerns for cartilage volume loss have been reported with repeated intra-articular steroid injections every 12 weeks over 2 years²²². At present, the clinical significance of this small difference in cartilage volume loss remains uncertain. For hyaluronic acid, the maximal pain reduction is reported for 2–4 injections at 3 months and 6 months in knee OA²²³.

Despite the short-term benefits of intra-articular therapies found for knee OA, a recent review of the efficacy and safety profiles of different

intra-articular therapies (steroids, hyaluronic acid, platelet-rich plasma, stem cells, prolotherapy) questioned their long-term effectiveness due to the lack of long-term data and methodological flaws²²⁴.

Based on limited efficacy and toxicity, acetaminophen, duloxetine and tramadol are only conditionally recommended for OA¹⁸³. Paracetamol reduces pain²²⁵ and improves physical function when compared to placebo²²⁶. Duloxetine (the centrally acting serotonin and norepinephrine reuptake inhibitor) improved WOMAC physical function subscale but failed to improve the WOMAC pain subscale with a higher incidence of adverse events when compared to placebo²²⁷. For knee or hip OA²²⁸, a high dose of tramadol provides pain reduction and functional improvement with higher gastrointestinal adverse events. Many other commonly used treatments, such as supplements (for example, glucosamine, chondroitin), vitamin D, opioids, bisphosphonates, colchicine, hydroxychloroquine, methotrexate, diacerein, acupuncture and arthroscopy, have not shown clinically meaningful benefit over placebo and/or can even be harmful^{181,183,215,229}.

Surgical interventions

Surgery can be considered for patients with advanced stages of structural (accessible via plain film radiographic changes) and symptomatic OA, given that the patient has been following appropriate first-line and second-line conservative options for more than 6 months³. There are several surgical options available for the treatment of OA, depending on the severity of the condition and the overall health of the patient. Osteotomy (cutting and altering the alignment of the bones adjacent to the affected joint) might be suitable in younger patients with unicompartmental disease. Joint replacement (removing the damaged part of the knee and replacing this with an implant) is a cost-effective option for patients with severe osteoarthritis of the knee or hip. Arthroscopic surgery is not recommended for the management of hip or knee OA.

Of note, an improvement in pain following TKR is not guaranteed. Patient dissatisfaction and poor outcome (perceived as long-term pain at 3 months to 5 years post-TKR) are reported in 10–34% of patients who underwent TKR^{230,231}. It is important to ensure that patients are aware of the potential for poor outcomes of surgical interventions (unfortunately, the majority are uninformed) and how they can optimize unfavourable outcomes. An improvement in pain (47 points on a 0–100 scale) has been reported in the first 12 months post-TKR but some pain and functional limitation typically persist in the long term²³². Compared to education and exercises, total hip arthroplasty provided greater improvements in pain and function over 0–100 HOOS-12 (Hip Disability and Osteoarthritis Outcome Score 12-item short form) subscores at 12-month follow-up²³³.

Quality of life

Global burden of disease

OA is a leading cause of disability and poor health-related quality of life (HRQoL), posing a significant individual and societal burden on persons and economies. OA accounts for 2.19% of all years lived with disability (YLDs) for any condition worldwide²⁰. It is the 14th highest cause of YLD worldwide. Further, OA affects one-third of persons aged 70 years or older and is among the top ten leading causes of YLD in this age group²⁰. In addition, the global age-standardized rates of YLD attributed to OA have increased by 9.5% from 1990 to 2020 (ref. 20). Knee OA, hand OA and hip OA account for 61%, 24% and 5.5% of YLD due to OA^{20,234}.

Primer

Table 2 | Effectiveness of pharmacological interventions on pain and function in osteoarthritis

Types of interventions	Comparator	Number of patients and number of trials included	Follow-up duration	Pain ^a	Function ^b	Level of evidence ^c	Ref.
Acetaminophen (paracetamol)	Placebo	2,072 patients, 5 trials	6–12 weeks	Not reported	0.13 SMD, 95% CI 0.00–0.26	Not reported	226
NSAIDs							
Topical NSAIDs	Acetaminophen	28,998 patients, 66 trials (pain); 22,914 patients, 16 trials (function)	4 weeks	-0.09 SMD, 95% CrI -0.55 to 0.37 ^d	0.29 SMD, 95% CrI 0.06 to 0.52	Not reported	219
			12 weeks	-0.20 SMD, 95% CrI -1.07 to 0.64 ^d	0.24 SMD, 95% CrI -0.29 to 0.79 ^d		
Oral NSAIDs	Oral NSAIDs	8,098 patients, 16 trials (pain); 7,979 patients, 16 trials (function)	4 weeks	-0.21 SMD, 95% CrI -0.58 to 0.16 ^d	0.03 SMD, 95% CrI -0.16 to 0.22 ^d	Not reported	220
			12 weeks	-0.05 SMD, 95% CrI -0.55 to 0.44 ^d	0.03 SMD, 95% CrI -0.33 to 0.37 ^d		
Oral NSAIDs	Placebo	17,861 patients, 48 trials (pain); 9,595 patients, 28 trials (function); 976 patients, 2 trials (pain and function)	2 weeks	-0.43 SMD, 95% CI -0.48 to -0.38	0.45 SMD, 95% CI 0.38 to 0.52	Not reported	220
			26 weeks	-0.21 SMD, 95% CI -0.39 to -0.03	0.19 SMD, 95% CI 0.07 to 0.3		
Intra-articular injections							
Corticosteroid	Intra-articular placebo	2 trials	≤6 weeks	-1.51 SMD, 95% CI -1.80 to -1.20	1.78 SMD, 95% CI 0.23 to 3.32	Not reported	221
			>6 and <24 weeks	-0.72 SMD, 95% CI -1.96 to 0.53 ^d	0.70 SMD, 95% CI 0.62 to 0.98		
Hyaluronic acid single injection	Intra-articular placebo	1 trial	3 months	-0.03 SMD, 95% CI -0.29 to 0.23 ^d	Not reported	Not reported	223
			6 months	-0.04 SMD, 95% CI -0.20 to 0.13 ^d	Not reported		
Hyaluronic acid 24 injections		6 trials	3 months	-0.76 SMD, 95% CI -0.98 to -0.53	Not reported	Not reported	223
			6 months	-0.36 SMD, 95% CI -0.63 to -0.09	Not reported		
Hyaluronic acid ≥5 injections		3 trials	3 months	-0.20 SMD, 95% CI -0.43 to 0.03 ^d	Not reported	Not reported	223
			6 months	-0.18 SMD, CI -0.35 to -0.01	Not reported		

CI, confidence interval; CrI, credible interval; NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardized mean difference, interpreted as <0.2, small effect; 0.5, medium effect; and >0.8, large effect. ^aFor the outcome of pain, a negative standardized mean difference indicates less pain following the intervention. ^bFor the outcome of function, a positive standardized mean difference indicates improved function following the intervention. ^cLevel of evidence assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) or specific criteria by the individual meta-analysis. ^dOutcomes that reached statistical significance.

Individual burden of disease

The direct costs of the disease can potentially be estimated as pharmacological, non-pharmacological or surgery expenses; however, the impact of their investment on the individual as a result of reduced pain, improved functionality and HRQoL is challenging to quantify

monetarily. The most disabling symptom a person with OA experiences is pain²³⁵. Pain, stiffness and limitation of joint movement reduce HRQoL. Approximately 80% of persons living with OA have limitations in movement and 25% cannot engage in their activities of daily life²³⁶. Although OA is perceived as a relatively ‘benign’ disease,

activity limitation and participation restriction are similar in both OA and rheumatoid arthritis²³⁷. Activity limitation also reduces social participation and might lead to social isolation, both intensifying over time with an increasing need for instrumental support (that is, housework, help with personal care and transport)²³⁸. General health, body pain, physical function, vitality, emotional role function, physical role function, social function and mental health in HRQoL were found to be significantly lower in persons with OA than in healthy persons. The impact was greatest in the dimension of physical function²³⁹.

Socioeconomic impact

While the direct costs of OA can be accurately estimated, data suggest that actual indirect costs are at least eightfold greater than direct costs²⁴⁰. Indirect costs due to reduced productivity at work, early retirement and sick days/absenteeism are a part of the economic burden of OA. Approximately 3.5% of persons aged 30–60 years (that is, in the working age group) experienced some symptoms of OA in 2020 (ref. 20).

The bulk of the lifetime direct cost of OA is due to surgery costs (for example, joint replacement) followed by medication, physician visits, physiotherapy and intra-articular injections²⁴¹. Persons with OA have higher rates of outpatient consultations, hospital admissions and all-cause mortality than those without OA²⁴². The cost of the disease may be higher in certain minorities, such as those with lower socio-economic status and women, some of whom are under-represented in cost estimates²⁴³. The costs are potentially higher in these groups as they present with later, more advanced disease²⁴⁴.

It is difficult to compare the health-care costs generated by OA as different countries have different health-care systems, currencies and workforce structures. The economic impact of OA, which includes direct and indirect costs, is substantial, ranging from 1% to 2.5% of the gross national product in countries with established market economies^{234,245}. In regions around the world, the average annual cost of OA for an individual was estimated between US\$700 and US\$15,600 in 2019 (ref. 234). The costs vary from country to country, with significant heterogeneity between studies^{246,247}. There is little data on indirect costs globally. Data from the USA show that estimated direct costs of patients with knee OA (US\$5,294–US\$5,704 per person per year) are twice those of patients without OA, and that assessable indirect costs such as work-related losses and homecare (US\$4,603 per person per year) are similar to direct costs²⁴⁸.

Presenteeism and work participation are impacted by pain, comorbidities, physically intensive work and low support from co-workers²⁴⁹. Therefore, the priority should be on the prevention of OA and careful planning of health-care services to handle the current and estimated future disease burden.

Prognosis and disease trajectory

Clinically, approximately two-thirds of patients have impactful symptom fluctuation (usually described as flares or episodes) on a background of symptomatic progression (constant background pain) that may be contradicted by the seeming stability of radiographic disease²⁵⁰. Pain and/or worsening functional limitations lead to negative impacts on HRQoL and participation and are leading considerations for the timing of joint replacement. Disease trajectories, as defined by symptomatic progression, are challenging to study in traditional cohorts. The relatively infrequent assessments in most cohort studies (for example, annual) limit the ability to evaluate shorter-term symptom fluctuations. Additionally, patients often accommodate their activities over

time to manage their level of pain and disability, and thus numerical rating scales and other pain measures may not be able to adequately capture the pain worsening²⁵¹. For example, data from the Osteoarthritis Initiative, a natural history cohort of individuals based in the USA with or at risk of OA, demonstrated relative stability of WOMAC pain over 5 years after an initial improvement that may reflect regression to the mean when entering a study²⁵². Similar findings were noted in another cohort for both pain and function²⁵³. In a systematic literature review comprising 21 studies that have used trajectory analyses to assess OA clinical outcomes, the trajectories were mostly stable over time, with the majority of patients reporting mild or low-moderate pain over time²⁵⁴.

Perhaps the most significant intervention in OA is joint replacement surgery. Knee replacement occurrence in the Osteoarthritis Initiative cohort data demonstrates a clear increasing trend over 6 years based upon Kellgren–Lawrence grading (KLG) status at baseline: 0.2% for KLG 0; 0.7% for KLG 1; 2.8% for KLG 2; 11.1% for KLG 3; and 32.9% for KLG 4 (ref. 46). KLG is used to assess radiographic severity of OA and patients are stratified into mild (KLG <2), moderate (KLG 2) and severe (KLG >2) knee OA. For comparison, estimates of lifetime risk of knee replacement in the general USA population were only 7% for men and 9.5% for women²⁵⁵. These estimates are similar to data from the UK, which also highlighted the low lifetime risk of joint replacement in the general population, with ~8–11% for the knee²⁵⁶. In 2013, another study analysing population-based registry data from five countries (Australia, Denmark, Finland, Norway and Sweden) demonstrated similar to slightly higher lifetime risks of knee replacement surgery, ranging from 6% to 15% for men and 10% to 23% for women²⁵⁷. However, among those with symptomatic OA, 52.2% of men and 50.6% of women in the USA were estimated to receive a primary total knee replacement in their lifetime²⁵⁵. In Spain, the lifetime risk of knee replacement after a general practitioner diagnosis of OA was estimated to be 30%²⁵⁸.

Overall, existing data support the relative stability of symptoms with only slow disease progression for the majority of patients living with OA. Nonetheless, while disease progression is not inevitable in OA, given the overall high prevalence of disease, even a minority or up to half of patients progressing to more severe disease sufficient for necessitating joint replacement surgery can have substantial public health impact and consequences for the HRQoL of an individual.

Outlook

OA can be considered a systemic disorder. Currently, the rates of disability due to OA are rapidly increasing worldwide, posing a significant challenge to health-care systems and society. Despite substantial progress in OA research and disease management, several issues remain formidable challenges, including exploring disease heterogeneity, identifying early-stage OA and developing effective DMOADs.

Key outstanding research questions

Firstly, there is currently no unified consensus on the classification of OA subtypes. Refining OA phenotypes and endotypes is of great significance for the exploration of disease mechanisms, selecting appropriate patients for precision clinical trials, and developing targeted management strategies and treatments²⁵⁹ (Fig. 4).

The second core scientific question is the staging of OA, especially the identification of early-stage OA. Traditionally, OA treatment begins upon the appearance of clinical symptoms, at which point the disease may no longer qualify as early stages and joint structural damage could already be irreversible. Leveraging big data-based machine

learning and artificial intelligence to identify early biomarkers makes the identification of early-stage OA possible²⁶⁰. Once early-stage OA is identified, the next challenge will be the development of effective early intervention measures and management strategies. Moreover, redesigning health systems to prioritize high-value care over low-value, often expensive options, is a critical shift needed to enhance patient outcomes and reduce unnecessary health-care costs.

Traditional studies that focus solely on cartilage, synovium or subchondral bone often fail to explain the full picture of pathogenesis observed during OA progression. Future research needs to emphasize the crosstalk among tissues within the joint and the remote regulation by organs outside the joint. In addition, it is essential to investigate pain, joint integrity and closely interconnected joint structures as a whole functional unit such as the cartilage–bone unit, synovium–fat pad unit and peri-articular muscles unit. Further in-depth research and understanding of the evolutionary law of these functional units in OA development and progression are expected to propose new molecular targets, paving the path for developing novel OA therapies. Lastly, using single-cell multi-omics and spatial omics approaches to study the spatiotemporal dynamics of diseased tissues based on OA classification and staging will significantly enhance our understanding of OA pathophysiology and help identify new key molecular targets.

Emerging treatments

In the OA research field, numerous innovative treatments are currently being investigated, each offering potential breakthroughs in how we approach this complex condition. DMOADs can include drugs that slow the progression of OA²⁶¹ as well as emerging treatments such as stem cell and gene therapy. Stem cell therapy, particularly by mesenchymal stem cells, holds promise by promoting cartilage regeneration and repair, regulating inflammatory microenvironment, and relieving joint pain due to their potential to secrete various growth factors and cytokines. These stem cells leverage their immunomodulatory and regenerative abilities to slow the progression of OA and enhance joint function^{262–264}. Stem cell therapy may work best in specific subsets of patients with OA. Individuals with early-to-moderate OA, who still have some structural integrity in their joint, may benefit more from regenerative therapies than those in advanced stages with significant osteophyte formation or bone remodelling. Specific protocols of stem cell therapy for OA still vary greatly with regards to cell source, cell dose, and mode of administration and additional research is still required.

Gene therapy represents another frontier, involving the repair or replacement of damaged genes using cutting-edge technologies such as CRISPR–Cas9. This approach not only targets the underlying genetic contributors to OA but also enables the delivery of specific genes, such as *FGF18*, *CX43*, *YAP* or *CBX4*, to support and enhance cartilage regeneration^{265–268}.

Addressing metabolic abnormalities in OA is another critical strategy in OA management. Targeting metabolic pathways (such as AMPK signalling) can protect chondrocytes and surrounding tissues, slowing the degradative processes associated with OA²⁶⁹. This approach aims to restore the balance of energy metabolism within the joint environment. Population studies have shown that antidiabetic drugs (such as metformin and GLP1 agonist) can reduce the long-term risk of joint replacement in patients with obesity or type 2 diabetes^{164,270}. Interventional studies aiming to assess the efficacy of repurposing these agents for slowing OA disease progression are ongoing^{271,272}.

Targeting gut microbiota may be another promising therapeutic strategy for patients with OA. Animal model and case–control studies

have unveiled changes in gastrointestinal microbiome composition reflecting reduced species diversity in patients living with OA, particularly in those with metabolic syndromes such as obesity^{273–276}. Analyses of 2,294 patients from the Rotterdam Study and Lifelines-DEEP studies revealed four bacterial clades associated with knee OA pain: *Bacilli*, *Lactobacillales*, *Streptococcaceae* and *Streptococcus*²⁷³. These bacterial species may alter gut permeability and release lipopolysaccharides into serum and synovial fluid, leading to a low-grade state of inflammation that accelerates OA progression²⁷⁷. Microbiome transplantation showed potential therapeutic effects in a mouse OA model²⁷⁸. A 6-month clinical trial of a prebiotic intervention for knee OA (NCT04172688) suggests that prebiotics are promising for conservative treatment of knee OA in adults with obesity²⁷⁹.

The search for safe, efficacious analgesics for OA is still ongoing. Ion channels expressed by nociceptors are attractive druggable targets. Active ongoing programmes target TRPV1 (intra-articular injection of ligands such as resiniferatoxin (NCT05248386)) or Na_v1.8 (NCT02660424). Interestingly, a study from 2024 reported that Na_v1.7, which is expressed by nociceptors, is increased in OA chondrocytes and that deleting the channel from chondrocytes resulted in attenuation of joint damage and associated pain behaviours in experimental OA²⁸⁰.

Joint distraction involves temporarily suspending joint surfaces to relieve pressure, allowing cartilage repair and reducing pain (reviewed in ref. 281). This technique can alleviate symptoms and delay the need for joint replacement. Advantages include preserving the natural joint and promoting intrinsic cartilage repair. However, the procedure is invasive and requires a period of limited mobility. Additionally, its long-term efficacy and the precise mechanisms of cartilage regeneration are still under investigation.

RNA-based therapies, including small interfering RNA for gene silencing, messenger RNA for gene supplementation, microRNA for gene regulation and CRISPR–Cas9 for gene edition, focus on modulating gene expression to prevent cartilage degradation and promote repair (reviewed in ref. 282). These therapies can target specific molecular pathways involved in inflammation and cartilage breakdown. The advantages lie in their precision and ability to directly modulate disease-related pathways. Challenges include delivery to the targeted joint tissues and ensuring stability and efficacy in the joint environment.

The discussed innovative therapies are at various stages of research and clinical trials. Each one offers unique mechanisms to tackle the multifaceted nature of OA. Together, they hold the potential to revolutionize OA treatment, providing new strategies to improve patient outcomes and their quality of life.

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- This Review highlights emerging classes of RNA-based technologies that hold potential for OA therapies.**

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Author contributions

Introduction (all authors); Epidemiology (all authors); Mechanisms/pathophysiology (all authors); Diagnosis, screening and prevention (all authors); Management (all authors); Quality of life (all authors); Outlook (all authors); overview of the Primer (D.J.H.).

Competing interests

D.J.H. is the editor of the osteoarthritis section for *UpToDate* and co-Editor in Chief of *Osteoarthritis and Cartilage*. D.J.H. provides consulting advice on scientific advisory boards for Haleon, TLCBio, Novartis, TissueGene, Sanofi and Enliven. A.-M.M. is co-Editor in Chief of *Osteoarthritis and Cartilage*. A.-M.M. provides consulting services or serves on advisory boards for Averitas, Orion, LG, Novartis and Eli Lilly. T.N. is a deputy editor of *Osteoarthritis and Cartilage* and provides consulting services for Novartis and Eli Lilly. All other authors declare no competing interests.

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