Osteoarthritis

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Osteoarthritis is a heterogeneous disorder that is increasingly prevalent largely due to aging and obesity, resulting in a major disease burden worldwide. Knowledge about the underlying aetiology has improved, with increased understanding of the role of genetic factors, the microbiome, and existence of different pain mechanisms. However, this knowledge has not yet been translated into new treatment options. New evidence has questioned the efficacy of recommended treatments, such as therapeutic exercise programmes and the focus on weight loss, but managing obesity and maintaining activity remain important for the prevention and management of osteoarthritis. Approaches should consider individual and cultural preferences and resource availability to increase patient and community engagement, and optimise outcomes worldwide. Most of the focus has been on established osteoarthritis where management is primarily directed at relieving symptoms. The search for the much needed effective treatments that improve both symptoms and structure, often referred to as disease-modifying osteoarthritic drugs, is ongoing. Promising data indicate that targeting inflammation is effective in hand osteoarthritis.

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Introduction

This Seminar discusses osteoarthritis, with a special focus on new developments over the last 5 years and gaps that remain. Most available data come from studies on knee and hip osteoarthritis, but increasingly, also from other common sites including the hand, shoulder, and ankle. Unfortunately, studies of the foot are scarce.

In this Seminar we present the data for current and emerging therapies with a focus on new evidence for their efficacy and effectiveness. Special attention is given to limitations of current therapies and barriers to implementation across different jurisdictions. Lastly, the importance of prevention and need for approaches that consider individual and cultural preferences, and resources availability, are considered.

Epidemiology and burden of disease

It is increasingly recognised that osteoarthritis is a worldwide health problem. A systematic analysis for the Global Burden of Disease Study estimated the prevalence in 2020 for symptomatic radiographically confirmed total osteoarthritis, and for osteoarthritis at specific joint sites, based on data from 204 countries and territories.[1] In 2020, 595 million people were estimated to have osteoarthritis worldwide of which those aged 30 years or older, 14·8% lived with osteoarthritis. The global age-standardised prevalence rate was 6973·6 per 100 000 people, with the highest estimates being for high-income Asia Pacific (8632·7), high-income North America (8431·7) and eastern Europe (7937·9), and with the lowest estimates being for southeast Asia (5677·4), eastern sub-Saharan Africa (5821·0) and central sub-Saharan Africa (5946·0). The global estimates were 4307·4 per 100 000 people for knee, 2226·1 for hand, 417·7 for hip, and 718·4 for other forms of osteoarthritis. The effect of osteoarthritis is considerable, as it was estimated as the seventh-ranked cause of years lived with disability for adults age 70 years and older. Both the prevalence and years lived with disability increased considerably from 1990 and will further rise (estimated to reach 1101·6 million individuals in 2050). The three regions with the greatest change are central, eastern, and western sub-Saharan Africa, with an estimated increase by more than 200%. The increase in these affected regions supports the notion that osteoarthritis also has great effect in low-income and middle-income countries (LMICs). Also other studies focused on LMICs (eg, China and India) using the Global Burden of Disease Study data, report increasing prevalence and effects.[2,3] These findings are in line with a systematic review of 34 studies over a 25-year period of people aged 15 years and older from south Asia, east Asia, the Pacific, and sub-Saharan Africa.[4] The systematic review showed a pooled prevalence of 16·05%, although with high heterogeneity,[4] indicating that one in six people had osteoarthritis. Given the increase in prevalence over the last years, this figure is likely an underestimation.

Societal costs because of medical costs and reduced work productivity due to osteoarthritis are high.[5] Detailed information is scarce. A systematic review including a large sample of studies since 2016 summarised annual osteoarthritis-related direct and indirect costs per patient. These costs varied greatly between countries and patient groups; however, differences in methodology between studies included in the review made comparison difficult. Moreover, all included studies were from high-income countries.[6]

Risk factors

Osteoarthritis is a heterogeneous disorder with a multitude of risk factors (figure 1).[7] Overweight or obesity is an important complex risk factor, which acts by joint

Search strategy and selection criteria

We searched PubMed for English literature from January 2019 with the term "osteoarthritis" in combination with "epidemiology in LMICs", "genetics", "gut microbiome", "pain", "diagnosis", "treatment", "obesity", "weight", "physical activity ", "exercise", "footwear", "NSAIDs", "tramadol", "opioids", "surgery", "prevention", "injury", and "mortality". We focused on systematic reviews and randomised controlled trials.

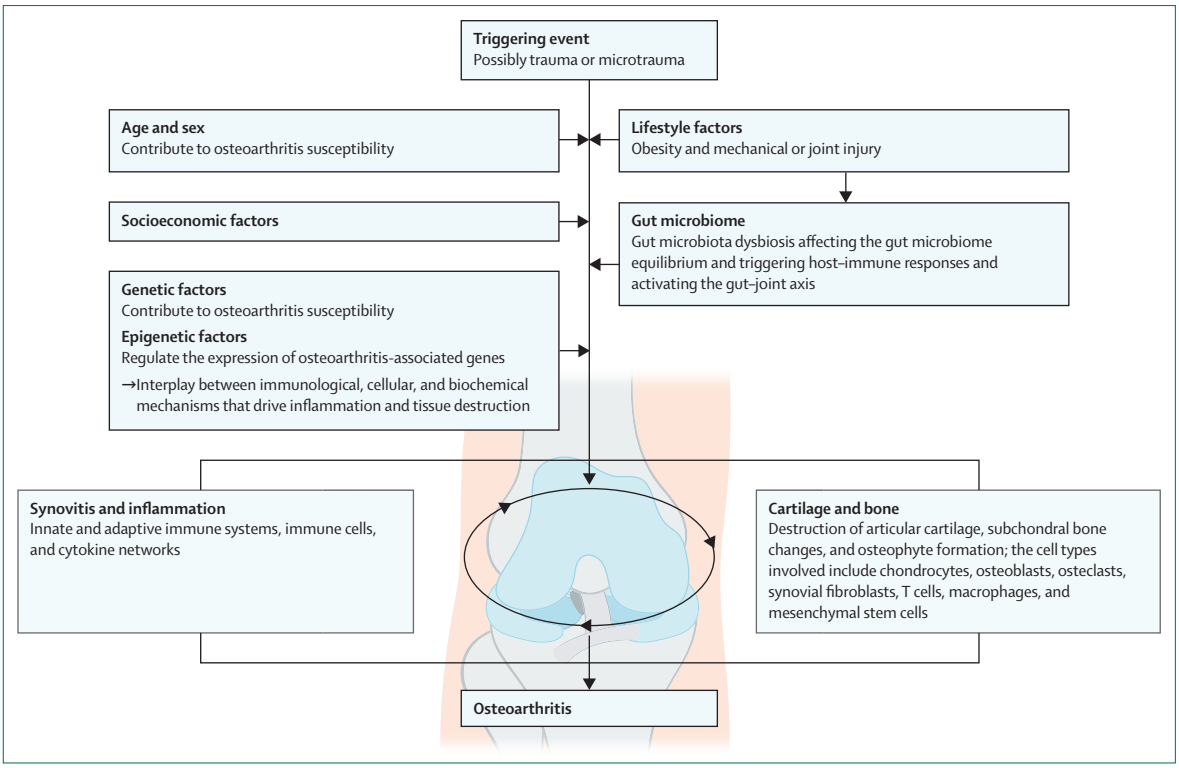

Figure 1: **Risk factors and potential contributing factors for osteoarthritis, and how they interact with each other**

overloading and other mechanisms. Particularly in women, sarcopenic obesity seems to play a role,[8] which aligns with a recent systematic review showing that weakness of the knee extensor muscle is associated with incident symptomatic and radiographic knee osteoarthritis,[9] further indicating the importance of maintaining muscle strength. Importantly, recreational physical activity was not associated with incident symptomatic radiographic knee osteoarthritis when examining after 5–12 years follow-up.[10] Obesity or overweight seems also to contribute to osteoarthritis by metabolic effects and low-grade inflammation, although the underlying causal mechanisms are not clear.[11] A recent meta-analysis did not support diabetes as a causal factor, since diabetes was not associated with incident osteoarthritis when BMI was accounted for.[12]

The heterogeneity of osteoarthritis has led to the concept of stratifying patients according to different phenotypes based on their risk factor profile, with the aim to provide personalised medicine in the era of precision medicine.[13] However, risk factors represent different pathological mechanisms that interact with each other and often coincide in patients.[7,14] An alternative to this concept is to define patients by the underlying molecular mechanisms or endotypes, which holds great promise, especially for drug development.[15]

Genetics

Familial risk factors are strongly associated, especially for spinal, hand, and hip osteoarthritis. A large genetic study, including more than 150 000 cases of osteoarthritis with different phenotypes, has elucidated an increasing number of frequent associating DNA variants.[16] These genetic variants have small effects on the disease, but are a powerful tool to identify pathogenetic mechanisms in osteoarthritis. Some of these genetic variants are associated with osteoarthritis at specific joint sites, while others overlap between joint sites, suggesting common pathologies.[16,17] A better understanding has come from integrating data from different sources, such as functional genomics, by which effector genes have been identified, and which have made clear that various underlying pathological processes are involved. Genes involved in skeletal development might be a major factor,[16,18] but genes also involved in joint degradation, signalling pathways, neuronal function and development, adipogenesis, muscle function, and immune response and inflammation could affect osteoarthritis.[16] Genetic correlations have also been seen with pain phenotypes.[16,17] These genes could be used to identify potential drug targets. Recent studies have focused on *ALDH2A1*, which is a gene associated with severe and erosive hand osteoarthritis[19] but also with many other phenotypes of osteoarthritis,[16] and is involved in retinoic acid metabolism. These studies elucidated the role of the *ALDH1A2* gene and retinoic acid in mechano-inflammation in the joint, but also as a potential target for modifying mechano-inflammation.[20] For screening of patients in clinical practice, these DNA variants are not suited but hold promise for the future.

Pathogenesis

Recent insights into the pathophysiology of osteoarthritis have shown a complex interplay between genetic and lifestyle risk factors with there being a growing interest in the potential role of the gastrointestinal microbiome (figure 1).[21,22] Genetic factors contribute to osteoarthritis susceptibility with recent studies highlighting the potential for epigenetic mechanisms to also regulate the expression of osteoarthritis-associated genes.[21] Together, these mechanisms result in an interplay between immunological, cellular, and biochemical mechanisms that drive inflammation and tissue destruction.[21] The trigger for these processes is thought to be a biomechanical injury or microtrauma that might interplay with genetic susceptibility and other environmental factors. These activated processes result in the pathological manifestation of osteoarthritis: destruction of articular cartilage, synovial thickening, subchondral bone changes, and osteophyte formation.[23] The cell types involved in these processes include chondrocytes, osteoblasts, osteoclasts, synovial fibroblasts, T cells, macrophages, and mesenchymal stem cells.[24] Innate immune cells, such as dendritic cells and macrophages and adaptive immune cells (eg, T-cell subsets, B-cell subsets, and natural killer cells), have considerable roles in pathogenesis, resulting in multiple proinflammatory immune mediators that regulate the expression of metalloproteinases and contribute to cartilage degradation and bone changes.[24]

The number of genes, pathways, and molecules with potential roles in osteoarthritis pathogenesis has grown substantially over recent years. The power of omics (genomics, proteomics, metabolomics, and single cell analyses) has been increasingly used to tackle these complex inter-relationships.[25] Studies have expanded from their traditional focus on cartilage and gene expression to other joint tissues, proteins, and metabolites. Single cell approaches provide unprecedented resolution and insights into the heterogeneity of cellular activities in osteoarthritis. Animal models of osteoarthritis provide the opportunity to validate functional changes and investigate underlying mechanisms so that omics findings can be linked to pathophysiology and potential therapeutic applications.[26] This complexity will be important to unravel to develop personalised approaches to the treatment and prevention of osteoarthritis.

Gastrointestinal microbiome

The gut microbiota is increasingly regarded as a multifunctional organ with a role in various immune, metabolic, and inflammatory functions.[27] There is some evidence that gut microbiota dysbiosis can break the host–gut microbe equilibrium, triggering host immune responses and activating the gut–joint axis and contributing to the pathogenesis of osteoarthritis. For example, it has been suggested that the gastrointestinal microbiome might be one of the factors triggering obesity-associated low-grade systemic inflammation, important in the pathogenesis of osteoarthritis.[28,29] Animal studies have shown links between obesity and increased severity of osteoarthritis and altered gut microbial DNA profile, with the use of prebiotics and probiotics in animal trials providing some proof-of-concept that modifying the gut microbiome might favourably modulate the progression of osteoarthritis.[30] However, current evidence from human studies is scarce. Shifts in the gut microbial profile and reduced gut microbial diversity have been identified in people with osteoarthritis. A recent systematic review showed differences in the gut microbiome in patients with osteoarthritis compared with healthy individuals, with evidence for differences associated with both worse and improved outcomes in osteoarthritis.[31] However conclusions about causation are restricted by substantial heterogeneity in the methodologies of studies examining this topic.[31]

Clinical presentation and diagnosis

The clinical presentation of osteoarthritis is well known. Some symptoms and signs are similar for osteoarthritis in all joint sites while others are joint-specific (figure 2). Osteoarthritis is often polyarticular in nature, which adds to its burden. Joint pain or discomfort upon activity is reported by patients as the main symptom. Previous pain and disability were considered as symptoms that inevitably would worsen. Group-based trajectory modelling has shown that the majority of patients experience a stable course, and some improve at long term.[36,37] Identifying the role of sudden-onset episodes of

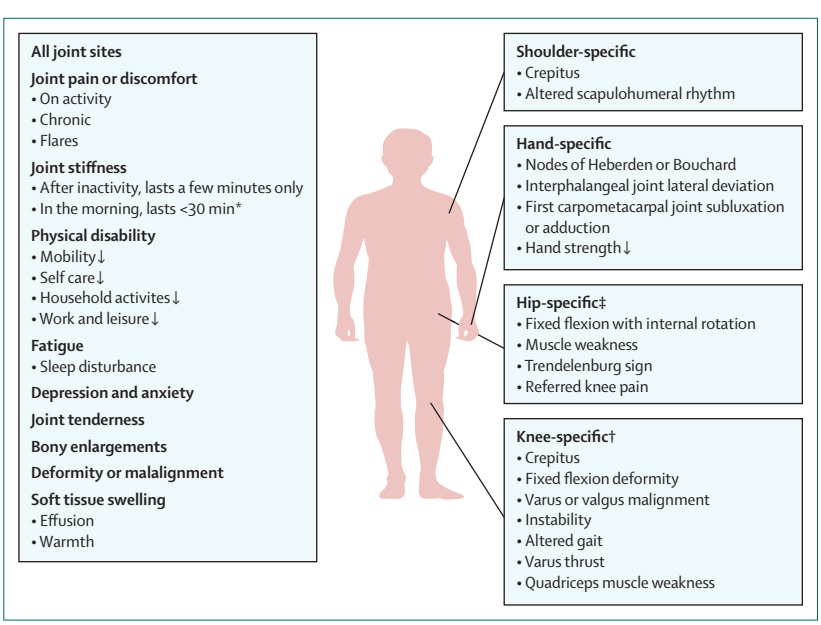

Figure 2: **Symptoms and signs in patients with osteoarthritis**
*Morning stiffness for more than 60 minutes does not preclude osteoarthritis.[32] †For knee osteoarthritis, crepitus, bony enlargement, tenderness of the bony margins of the joint, and joint pain on movement; can be assessed with fair to excellent reliability.[33,34] ‡A systematic review showed that tests of hip motion, such as squatting, abduction, adduction, internal rotation, and observing hip or groin pain during that motion could indicate hip osteoarthritis.[35]

increased pain (ie, flares) and whether to consider osteoarthritis as an acute-on-chronic disease needs further investigation[38] to inform patients about their prognosis and direct treatments.

Pain is multidimensional and multifactorial and can be felt in the osteoarthritic joint and beyond the joint,[39] and can best be understood by the biopsychosocial model. Nociceptive joint pain can originate from local tissue processes and damage, such as mild synovitis, increased subchondral bone turnover, periosteal stress via bony enlargements, distended joint capsule, and extra-articular structures including bursitis, tendinitis, or tension on ligaments. Although degradation of cartilage, which is not innervated, is not a source of pain, accompanying vessel and nerve ingrowth can be.[40]

Many patients also have neuropathic-like pain symptoms—also called nociplastic pain—such as allodynia and hyperalgesia with tingling, numbness, and burning sensations.[41] These symptoms are thought to arise from altered nociception due to dysfunction or sensitisation of the somatosensory system, including the nociceptor pathways itself, and contribute to chronic pain.[39] A systematic review estimated the prevalence of neuropathic-like pain or pain sensitisation to be up to 40% in knee or hip osteoarthritis depending on the questionnaire used or the cohort.[42]

Many studies have shown that psychosocial factors, such as the patient's perception of their osteoarthritis, coping strategies, comorbidities (ie, depression and anxiety), and socioeconomic status play an important role in pain and disability.[43]

Diagnosis and imaging

It is now generally accepted that a clinical diagnosis of osteoarthritis is sufficient to initiate treatment and can be made based on symptoms, history of risk factors, and signs on physical examination.[44] Laboratory testing and imaging are not needed for diagnosis.

Imaging needs to be carefully integrated into the overall management of the disease. Imaging is now considered not necessary in cases where the clinical diagnosis is clear. However, imaging can be used to exclude other causes, for instance when symptoms or signs are atypical, symptom intensity is high, the disease course rapid, or recent trauma has occurred. Radiographs are then usually the first choice (appendix). In patients who have not had any previous imaging performed, there could be strong patient expectations for assessment of their painful joints with imaging. These expectations, influenced by local expectations on what is appropriate health care, need to be considered in decision making. Repeated imaging should be avoided as changes in the joint occur slowly. Unnecessary imaging has the potential to increase costs and delay implementing management plans that could benefit the patient.

See Online for appendix

Contrast imaging has an important role in osteoarthritis research. Imaging modalities such as MRI (appendix) have transformed our understanding of the pathogenesis of osteoarthritis and underpin current research endeavours aimed at better phenotyping joints so that therapies can be targeted more effectively.[45] There is strong evidence that structural changes such as bone marrow lesions seen using imaging are associated with joint pain and the progression of osteoarthritis,[46] and have potential to phenotype patients more effectively for trials of osteoarthritis and as targets for treatment.[46] However, there is currently no data to suggest such imaging changes have a role in clinical practice.

In some countries, musculoskeletal ultrasonography is used to complement physical examination in rheumatology practice.[47] Musculoskeletal ultrasonography can be useful for detecting inflammatory and structural changes in patients with joint pain without obvious joint swelling, in differentiating various inflammatory diagnoses (eg, osteoarthritis, psoriatic arthritis, and crystal arthropathies), in monitoring inflammatory arthritis, and for interventional procedures. Although changes of osteoarthritis can be detected using ultrasonography,[48] its role in clinical care remains unclear.

Management

To date, there are no specific disease modifying anti-osteoarthritic treatments. Current management of patients with osteoarthritis aims to improve patient and societal outcomes by reducing symptoms and improving function. Clinical guidelines (table 1) broadly recommend the provision of effective and individualised information, combined with non-pharmacological and pharmacological interventions, and when these are insufficient, surgery.[44,49–53] High-quality evidence is available but not for all treatment options, which might explain the differences between guidelines that are also based on opinions of experts and patients.

Non-pharmacological treatments

Education

Educating patients about osteoarthritis is important for managing expectations and improving outcomes. However, the best way to deliver this education remains unclear. A systematic review found that few educative interventions identify learning objectives, are based on theory, use previous research or codesign principles, or cover a broad inconsistent range of topics.[54] A scoping systematic review found that patients want more information about the diagnosis of osteoarthritis, its effects on daily life and its long-term prognosis, and non-pharmacological and pharmacological treatment options.[55] Furthermore, patients wanted the information to be delivered in a clear way, from a variety of health information sources, and with different modes of delivery relevant to the patient context.

Effective, patient-centred communication is fundamental to optimal health outcomes and needs to be individualised and responsive to patient health

concerns, beliefs, and contextual variables.[56] Achieving patient-centred care and communication is complex as there could be institutional, communication, environmental, and personal and behavioural related barriers that need to be identified and considered in clinical interactions.[56]

Although digital and mobile technologies have the potential for providing patients with reliable and accessible information, their effectiveness in osteoarthritis remains unclear. A recent scoping systematic review found that although individual small-scale studies highlighted promising short-term effects of mobile health technology in self-managing hip and knee osteoarthritis, many mobile health technologies were developed without clinicians' or patients' contributions.[57] A recent trial that addressed these limitations and examined a combined digital technology programme consisting of an exercise app, fitness tracker, and online health coaching, found no clinically meaningful reduction in knee pain after knee replacement at 3 months compared with the usual care.[58] Long-term benefits and cost-effectiveness, user experience, needs and expectations, and cross-cultural adaptation of these technologies will need to be considered in future developments.

Weight loss

Most guidelines recommend weight loss as a core management focus in those with knee and hip osteoarthritis who are overweight or obese.[44,50,51,53] Data from a meta-analysis showed that weight loss of 5–10% of total bodyweight had a modest effect on knee pain (standardised mean difference 0·33).[59] Loss of 10% or more of total bodyweight is needed to have any considerable effect on knee pain.[60,61]

Targeting obesity in osteoarthritis is important, but repeated lack of success can negatively affect individuals and needs to be considered in patient discussions, as most patients are aware that weight contributes to osteoarthritis and have tried unsuccessfully to lose weight.[62] 50% of patients who are overweight or obese report weight stigma and feeling blamed for not getting better, which contributes to maladaptive coping mechanisms that exacerbate

	EULAR update (2018)[49]	ACR update (2019)[50]			NICE update (2022)[44]	AAOS (2021 and 2023)[51,52]	
	Hand	Hand	Knee	Hip	All	Knee	Hip
Non-pharmacological treatment							
Education, including self-management principles	√	√	√	√	√	√	..
Weight loss	..	..	√	√	√	√	..
Exercise	√	√	√	√	√	√	↔
Canes or walking aides	..	..	√	√	↔	↔	..
Knee brace	..	..	√, tibiofemoral	..	↔	↔	..
Thumb base orthosis	√	√	..	..	↔	..	..
Hand or finger orthosis	X	↔	..	..	↔	..	..
Modified shoes	..	..	X	..	..	..	..
Wedged insoles	..	..	X	X	↔	X	..
Acupuncture	..	↔	↔	↔	X	↔	..
Manual therapy	..	..	X	X	↔	↔	..
Massage	..	..	X	X	..	↔	..
Pharmacological treatment							
Oral NSAIDs	√	√	√	√	↔	√	√
Topical NSAIDs	√	↔	√	..	√ knee, √ other	√	..
Intra-articular corticosteroids	↔	↔	√	√	↔	↔	↔
Paracetamol	↔	↔	↔	↔	↔	√	↔
Duloxetine	..	↔	↔	↔	..	..	..
Weak opioids and tramadol	↔	↔	↔	↔	↔	X	X
Disease modifying anti-rheumatic drugs and biologicals	X	X	X	X	..	..	..
Platelet-rich plasma	..	..	X	X	..	↔	..
Hyaluronic acid injections	..	X	X	X	X	X	X

AAOS=American Academy of Orthopaedic Surgeons. ACR=American College of Rheumatology. EULAR=European Alliance of Associations for Rheumatology. NICE=National Institute for Health and Care Excellence. NSAIDS=non-steroidal anti-inflammatory drugs. √=should be recommended. ↔=can be considered. X=should not be recommended.

Table 1: **Overview of recommendations from various guidelines**

obesity.[63] 50% of women with overweight or obesity report not attending a medical appointment where they might be weighed.[64]

Weight loss might result in stigma as it is associated with illness in some countries, contributing to the complexity of tackling obesity in some low-income transitioning communities. New developments in weight loss drugs such as the GLP-1 receptor agonist might have a role in weight loss and osteoarthritis.[65]

Exercise

Guidelines consistently recommend therapeutic exercise for knee, hip, and hand osteoarthritis.[44,49–53] However, a systematic review and meta-analysis of 31 randomised controlled trials that examined the effect of therapeutic exercise in knee and hip osteoarthritis found a small effect of questionable clinical importance on pain and physical function at 3 months that was even smaller at 6 and 12 months,[66] but with limited evidence of benefit in patients with more severe pain and poor physical function. Therapeutic exercise interventions were defined as physical activity that is planned, structured, repetitive, and purposeful for improvement or maintenance of a specific health condition, and so, includes most of the well recognised programmes. When strength training for knee osteoarthritis was examined in a trial comparing high-intensity and low-intensity strength training and attention controls, equal improvements in pain in all three groups were found.[67] These findings question the focus on therapeutic exercise programmes for the management of osteoarthritis, but also highlight the importance of exercise and physical activity in osteoarthritis.

Physical activity is important for decreasing osteoarthritis pain and improving physical function and health related quality of life.[68] People with lower-extremity osteoarthritis should be encouraged to engage in achievable amounts of physical activity of even modest intensities. It is important to keep physically active rather than focusing on specific types of exercise. Over-reliance on therapeutic programmes has the potential to divert resources from approaches that might better suit patients with osteoarthritis in different resource settings. Even where programmes are free, barriers such as time to attend appointments and difficulties with inadequate and unreliable transportation might affect the most susceptible people in the community.[69] A study in South Africa highlighted the absence of facilities and equipment for exercise programmes as barriers to physical activity, which constitutes intentional exercise conducted in one's leisure time.[70] Too often the benefits of physical activity such as walking as part of activities of daily living, is underestimated despite it being low cost, feasible, acceptable, and accessible across populations.[71,72] Programmes such as The Walk With Ease Program[73] were developed to help people with arthritis learn to exercise safely, improve symptoms, and offers good value for otherwise inactive or insufficiently active individuals.[74] Adherence to physical activity remains a major challenge with the relevance of enjoyment of exercise being examined as to how it might help to advise people with arthritis about exercise.[72]

Other non-pharmacological treatments

Orthoses and canes or walking aids can be considered for reducing pain and improving physical function.[44,49–51,53] For acupuncture and manual and massage therapy, efficacy is less clear and inconsistently recommended.[44,50,51] Adapted footwear or wedged insoles were not effective in randomised clinical trials.[75,76] Although there remains uncertainty about the use of knee bracing,[77] guidelines recommend its use for symptom control,[44,50,51] and there is some evidence that splinting might benefit base-of-thumb osteoarthritis.[78] More work is needed to establish the efficacy of splinting and bracing of the foot and ankle for osteoarthritis.

Coordinated multidisciplinary care

Although there have been calls by experts for coordinated multidisciplinary care in osteoarthritis, numerous well-designed programmes have only shown modest benefits. One study focusing on general practice pathways in the UK and involving practice nurses and general practitioner care found no effect on patient-reported outcomes after 6 months.[79] A randomised controlled trial examining a primary care service delivery model for knee osteoarthritis found that although knee pain and function improved more compared with usual general practitioner care, it was unlikely to be clinically meaningful.[80] Patient empowerment is important for patient-centred care, but explorative analysis of those in primary health-care in Sweden undertaking Supported Osteoarthritis Self-Management for 3 months found that patient empowerment improved from baseline to the 3-month follow-up, but no change to 9-month follow-up.[81] Living alone was associated with less improvement in empowerment. More work is needed to ensure that programmes are effective, equitable, culturally appropriate, and acceptable to ensure high levels of engagement to optimise outcomes in a cost-effective way.

Pharmacological treatments

Currently, only drugs to reduce osteoarthritic pain are approved for osteoarthritis. Evidence of the last years have increased our knowledge of their efficacy, which is unfortunately not high at the group level, and of their safety, which is reflected in the recommendations of various guidelines (table 1).

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely recommended for osteoarthritis,[44,49–53] and due to their favourable safety profile,[82] topical NSAIDs are now the first choice for treatment for hand and knee

osteoarthritis. Topical NSAIDs have restricted systemic exposure and all-cause mortality, cardiovascular diseases, and gastrointestinal bleeding are at lower risk compared with paracetamol and oral NSAIDs.[83] Topical NSAID efficacy is similar to oral NSAIDs for pain relief. In a large network meta-analysis, effect size for pain was up to 0·64 for topical diclofenac.[84] Effects sizes differed per oral NSAID, and most efficacious were diclofenac at 150 mg per day (effect size 0·56) and etoricoxib at 60 mg per day (effect size 0·65).[84] However, gastrointestinal, renal, and cardiovascular adverse effects restrict the use of oral NSAIDs, hence they are recommended in the lowest effective dose for short periods of time.[49,50] In contrast to oral NSAIDs,[85] topical NSAIDs are underappreciated and underused[86,87] and could be used more.

Intra-articular corticosteroids

Intra-articular corticosteroids can be considered for short-term pain relief in patients with knee and hip osteoarthritis (adjusted effect estimate compared with placebo –11·85 on 0–100 scale).[44,50–53,88] Injections do not seem to be associated with an increased incidence of total knee replacements or radiographic progression,[89,90] although experts recommend that frequent repeated injections should be avoided.

Paracetamol, tramadol, and strong opioids

Paracetamol is now only recommended when NSAIDs are contraindicated for short-term use[44,49–52] due to its small beneficial effect on pain (effect size 0·15).[84] Tramadol is often used for osteoarthritis pain relief[85,91] and following the standard recommendations can be considered,[44,49,50] although a Cochrane review indicated no important benefit on pain reduction compared with placebo (4% absolute improvement) and a greater risk of adverse events.[92] Moreover, two large observational studies reported a higher risk of all-cause mortality[93,94] and cardiovascular diseases.[94] As such, tramadol recommendation should be reconsidered whereas strong non-tramadol opioids are not recommended.[44,50–52]

Duloxetine

Antidepressants, especially the serotonin-noradrenaline reuptake inhibitor duloxetine, can be considered for some patients with osteoarthritic pain.[50] A Cochrane review reported a small positive effect on pain (mean

	Target of treatment	Osteoarthritis phenotype	Primary outcome	Efficacy (score, 95% CI)	Comments
Prednisolone[96]	Inflammation	Inflammatory finger	Pain at 6 weeks (VAS)	–16·5 (–26·1 to –6·9); p=0·0007*	Effect on synovial thickening by ultrasonography
Topical betamethasone diproprionate[97]	Inflammation	Hand	Pain at 6 weeks	No	..
Methotrexate[98]	Inflammation	Erosive hand	Pain at 3 months	No	Some effects on radiographic progression at 12 months
Methotrexate[99]	Inflammation	Inflammatory hand	Pain at 6 months (VAS)	–9·9 (–19·3 to –0·6); p=0·037*	..
Hydroxychloroquine[100]	Inflammation	Erosive inflammatory hand	Pain and function at 52 weeks	No	No effect on radiographic progression at 52 weeks
Colchicine[101]	Crystal induced inflammation	Hand	Pain at 12 weeks	No	..
Colchicine[102]	Crystal-induced inflammation	Hand	Pain at 12 weeks	No	..
Lutikizumab[103]	IL-α/β	Inflammatory knee	Pain at 16 weeks	No	No effect on synovitis or structure at 52 weeks
Lutikizumab[104]	IL-α/β	Erosive inflammatory hand	Pain at 16 weeks	No	No effect on synovitis or structure at 26 weeks
Otilimab[105]	Granulocyte macrophage-colony stimulating factor	Inflammatory hand	Pain at 6 weeks	No	..
Tocilizumab[106]	IL-6	Hand	Pain at 6 weeks	No	..
Zoledronic acid[107]	Bone turnover	Knee with bone marrow lesion	MRI-cartilage volume change at 24 months	No	No effect on pain
Denosumab[108]	Rank ligand	Erosive hand	Erosive progression at 24 weeks (GUSS)	8·9 (1·0 to 6·9); p=0·024*	No effect on pain
Metformin[109]	Glucose metabolism	Knee overweight or obese	Patient reported outcomes at 4 months (KOOS)	Total p=0·0001; symptoms not significant; pain p=0·0001; activity of daily living p=0·0001; sport or recreation p=0·0001; quality of life p=0·003*	..
Liraglutide[110]	Glucagon-like 1 receptor	Knee overweight or obese	Pain at 52 weeks	No	Weight loss in both groups in pre-randomisation period; liraglutide resulted in significant weight loss

GUSS=Ghent University scoring system. KOOS=knee injury and osteoarthritis outcome score. VAS=visual analogue scale. *Difference between the groups (95% CI), p-value between groups.

Table 2: **Randomised placebo-controlled double-blind trials of repurposed drugs and supplements in patients with osteoarthritis since 2019**

	Target	Type of drug	Way of delivery	Primary effect	ClinicalTrials.gov identifier
RXT-GRT7039, resiniferatoxin	TRPV1 agonist	Derived from capsaicin	Intra-articular	Pain	NCT04885972, NCT05248386, NCT05449132, NCT5377489
GSK3858279	CCL17 blockade	Monoclonal antibody	Intravenous or subcutaneous	Inflammatory pain	NCT0583842
LY3857210	P2X7 inhibitor	Small molecule	Oral	Peripheral and CNS pain	NCT05620563, NCT05986292
LY3526318	TRPA1 antagonist	Small molecule	Oral	Pain	NCT05080660, NCT05986292
LY3556050	Somatostatin receptor type 4 agonist	Small molecule	Oral	Inflammatory and mixed pain	NCT04627038, NCT05986292
LY3016859, fepixnebart	Epiregulin and TGFα inhibition	Monoclonal antibody	Intravenous or subcutaneous	Pain	NCT04456686, NCT05986292
TissueGene-C Invossa	Allogeneic human chondrocytes and cells modified to overexpress TGF-β1	Gene and cell therapy	Intra-articular	Cartilage repair	NCT03291470, NCT03203330, NCT05276011
ICM-203	Recombinant adeno-associated virus vector expresses therapeutic gene	Gene therapy	Intra-articular	Cartilage formation and reduction of joint inflammation	NCT04875754, NCT05454566
QUC398, M6495	Anti-ADAMTS-5	Nanobody	Subcutaneous	Cartilage preservation	NCT05462990
LNA043	Modified ANGPTL3 protein acting on cartilage-resident cells	Recombinant human protein	Intra-articular	Cartilage regeneration	NCT04864392, NCT04814368
DFV890	NLRP3 inhibitor	Small molecule	Oral	Anti-inflammatory	NCT04886258
RHH646	Unknown	Small molecule	Oral	Cartilage regeneration	NCT05816395
LRX712	Drives cartilage stem and progenitor cells differentiating into chondrocytes	Small molecule	Intra-articular	Cartilage regeneration	NCT03355196

Table 3: **New drugs under investigation in randomised placebo-controlled trials**

difference 0·59; 0–10 scale) and efficacy lasting up to 16 weeks, while there was no difference in serious adverse events between the groups.[95] Future research should investigate which patients will benefit most from the treatment.

New developments

Repurposed drugs

Several existing drugs that were originally developed for other purposes have been investigated for efficacy in osteoarthritis (table 2). There is special interest in anti-inflammatory drugs known for efficacy in diseases such as rheumatoid arthritis or gout, since synovial inflammation has been recognised as clinically relevant in osteoarthritis[111] and crystals have been shown in osteoarthritic joints.[112] Many of these studies were performed in patients with hand osteoarthritis, since in this non-weight-bearing phenotype, mechanisms other than mechanical loading are considered to play a major role.

Trials investigating biologicals targeting pro-inflammatory cytokines did not show an effect on short to midterm pain outcomes,[103–106] which challenged the concept that inflammation plays a major role in osteoarthritic pain. However, a placebo-controlled trial investigating 10 mg prednisolone daily reduced pain,[96] although its adverse effects prevent long-term use. The concept was further supported by a placebo-controlled trial with methotrexate showing a pain-reducing effect.[98]

Trials with colchicine, a cheap and safe drug, showed no effect on short-term symptom relief.[101,102] Long term use of these treatments could be efficacious, as suggested by post-hoc analyses from two large randomised controlled trials that investigated the blockade of IL-1 and colchicine in patients with cardiovascular diseases. These trials showed a lower incidence of total knee and hip replacements over placebo.[113,114] Future long-term trials, including structural end points, are warranted.

Since increased bone turnover (as visualised in bone marrow lesions) has been shown to be clinically relevant in osteoarthritis,[111] drugs used in osteoporosis seem promising.[107] However, zoledronic acid was not efficacious in patients with knee osteoarthritis with a high rate of bone turnover on pain or structure outcomes.[107] In contrast, denosumab was superior to placebo in erosive inflammatory hand osteoarthritis on radiographic outcomes.[108] This study holds promise for the future, although the adverse effects on bone health after discontinuation could be a limitation. Drugs such as metformin (a somewhat safe drug) and GLP-1 receptor agonists (used for type 2 diabetes and weight loss) are gaining interest for their potentially beneficial effects in osteoarthritis.[115,116] A placebo-controlled trial indicated an effect of metformin on symptoms in patients with knee osteoarthritis and overweight or obesity.[109] For GLP-1 receptor agonists, promising results came from an observational study in patients with knee osteoarthritis with comorbid type 2 diabetes, which showed that those on a GLP-1 receptor agonist had less pain, less cartilage loss, and a lower incidence of knee surgery than those not receiving a GLP-1 receptor agonist.[65] However, a placebo-controlled trial showed no efficacy of liraglutide on knee pain.[110] Moreover, adverse effects of GLP-1 receptor agonists might restrict their long-term use, for which further research is needed.

New drugs

There is interest for new analgesic drugs (table 3). Specific areas of promise are the nerve growth factor (NGF) pathway (which can be modulated by blocking monoclonal antibodies and tropomyosin-related kinase

inhibitors) and transient receptor potential vanilloid 1 (which is well known for its agonist capsaicin).[39] Unfortunately, NGF blockade by monoclonal antibodies did not only show pain relief, but also rapid progressive osteoarthritis and an increased number of joint replacements.[117]

Many new promising disease-modifying drugs aimed at prevention of cartilage loss or regeneration of cartilage, or at modifying subchondral bone remodelling, have been developed (table 3). To be approved, these drugs have to also improve symptoms. Intra-articular anabolic recombinant human fibroblast growth factor 18 in a long-term randomised controlled trial preserved cartilage, but had no effect on pain.[118] Similarly, an oral anti-catabolic inhibitor of cathepsin K showed a beneficial effect on cartilage and bone after 24 weeks, however no effect on symptoms.[119] Lorecivivint, a CLK/DYRK kinase inhibitor thought to modulate both inflammatory and Wnt signalling pathways, could not help patients reach the primary endpoint, but showed efficacy on pain and radiographic progression in a subgroup of patients with unilateral symptomatic knee osteoarthritis.[120] These examples highlight the importance of future studies that help us understand the (adverse) effects of pain reduction, how structure modification and pain alleviation align, and optimal trial design.

Other intra-articular treatments

Intra-articular platelet-rich plasma (PRP) is not consistently recommended despite its wide use due to the absence of evidence. Recently, two high-quality randomised trials in patients with ankle and knee osteoarthritis did not show superiority of PRP over intra-articular saline, thus supporting the recommendation against its use.[50,121,122] Other treatments, such as dextrose prolotherapy and hyaluronic acid injections, both lack solid evidence, and are not recommended.[44,50–52] Furthermore, to date there is no clear evidence for efficacy of therapies such as stem cells, that are widely used in some countries and are not recommended.[50,123]

Surgery

When symptoms of knee or hip osteoarthritis greatly affect the quality of life and non-pharmacological treatments have been ineffective, joint replacement should be considered. The lifetime risk for a patient diagnosed in primary care with knee or hip osteoarthritis is estimated at 30% or 14%, respectively.[124] Younger patients are particularly at risk, with surgery common in the second year after diagnosis. Although this operation relieves pain and improves function, up to 25% are to some extent dissatisfied with the result.[125] Risk factors include patients catastrophising, worse pain, neuropathic-like pain or pain sensitisation, and patient future expectations regarding post-operative kneeling or psychological wellbeing. In contrast, worse pre-operative radiographic osteoarthritis correlates with less pain after surgery.[125–127] Also, in patients with a high BMI, replacement is effective, but they have more complications. A US-based study showed that in patients with a BMI over 40 kg per m² and multiple comorbidities (eg, cardiovascular diseases or diabetes), a knee replacement was a good treatment option from a cost-effectiveness perspective.[128] Guidelines recommend that BMI might not be a barrier for joint replacement surgery, but it is crucial that expectations, harms, and risks are discussed with the patient pre-operatively.[44]

Joint replacement is also recommended for shoulder osteoarthritis.[44] A Cochrane review only found randomised trials comparing different types of shoulder replacements and different techniques,[129] and due to low quality, could not conclude which is most effective. High-quality trials are needed.

End-stage ankle osteoarthritis can be treated with either joint replacement or arthrodesis, but it is unclear which is superior.[130] In a randomised controlled trial where joint replacement was compared with arthrodesis, 21% of 303 patients had at least one serious adverse event, with more wound healing issues in the replacement group and with more thromboembolic events and non-union in the arthrodesis group. After 52 weeks, joint replacement was not superior to arthrodesis in symptom alleviation.[131]

Information on survival rates of joint replacement is of importance in clinical decision making and counselling of patients. These data can be obtained from long-term follow-up data from registries. Based on an Australian and Finnish registry data (of 299 291 total knee and 215 676 hip replacements), the risk of all-cause construct survival was estimated at 93·0% (95% CI 92·8–93·1) at 15 years and 82·3% (95% CI 81·2–83·2) at 25 years for knee replacements, and 89·4% (95% CI 89·2–89·6) at 15 years and 57·9% (95% CI 57·1–58·7) at 25 years for hip replacements.[132,133] Based on 2725 ankle replacements, the 5-year survival was estimated at 90·2% (95% CI 89·2–91·1).[134] The survival rate for unicompartmental knee replacement was lower than total knee replacements (all-cause construct survivorship of 69·8% [95% CI 67·6–72·1] at 25 years).[133,135]

Denervation

Increasingly, nerve innervating hand or knee joints are targeted directly in an attempt to relieve pain. A systematic review with low-quality evidence (predominantly case reports) showed efficacy of surgical denervation of osteoarthritic hand joints,[136] but also considerable adverse events. Genicular nerve blockade is performed pharmacologically[137,138] or by radiofrequency ablation, which shows short-term knee pain relief. Only radiofrequency ablation is conditionally recommended by the American College of Rheumatology,[50] despite the heterogeneity of techniques and controls and the absence of long-term safety data for which future research is warranted.

***Panel*: Future perspectives**

Osteoarthritis is a complex disease resulting from an interplay of person-related and joint-specific risk factors. Future research will need to address osteoarthritis in the shoulder, ankle, foot, and temporomandibular joints where, to date, there has been little research. Developing classification criteria will enable elucidation of the burden and risk factors for osteoarthritis at these sites, providing a sound basis for developing and testing interventions aimed at improving outcomes.

Ongoing monitoring of the global prevalence, incidence, and effect of osteoarthritis will be important to raise and maintain awareness among the community and for policymakers to ensure adequate resources are available for the implementation of effective therapies and research for the development of new treatments.

There is ongoing translation of evidence-based approaches to managing important risk factors for osteoarthritis, including obesity and physical activity, with the focus being working with patients and communities to provide effective, culturally appropriate care. Future research is warranted to re-evaluate how best to target physical activity and obesity. How, and in whom, can strategies be successful? What are other options? To target obesity, we need to focus on achievable goals that include slowing weight gain over adult years, and consider the use of pharmaceuticals to complement lifestyle programmes. To target low activity, we need to broaden our approach for exercise to include incidental activities and walking, making this exercise accessible to more people and increasing adherence.

Ongoing research is needed to increase our understanding of the underlying pathological mechanisms of osteoarthritis in the setting of the complex interactions between genomics, proteomics, and metabolomics to develop better targeted personalised treatments.

Pain is a key symptom for patients with osteoarthritis. Further elucidating pain mechanisms and pain phenotypes in osteoarthritis can facilitate the development of new effective treatments. It is important to also focus on the unwanted adverse effects of new pain treatments.

The osteoarthritic process results in considerable joint damage. Future research investigating new disease-modifying osteoarthritic drugs should focus on the translation of a disease-modifying effect to outcomes that are relevant for patients.

As osteoarthritis develops and evolves over the life course, prevention should play a key role. We need to identify at-risk patients and develop a better understanding of osteoarthritis in the community and develop primary prevention activities in society that are acceptable and accessible to most people and reduce the overall individual and societal burden.

Preventing death from cardiovascular disease in osteoarthritis

All-cause mortality is increased in people with osteoarthritis.[139] Cardiovascular disease is the most common cause of death and mortality is increased by 24% compared with those with osteoarthritis in the general population.[140] As people with osteoarthritis have a higher prevalence of hypertension, obesity, dyslipidaemia, and diabetes compared with the general population,[141] improved management of cardiovascular risk factors is important to reduce mortality rates in those with osteoarthritis.

Prevention

Osteoarthritis is a condition that develops during the life course and its prevention needs the targeting of risk factors across decades. Future approaches that include personalised risk assessment, including genetic risk, might be more effective. Also, as our understanding of osteoarthritis pathogenesis increases, the potential importance of some risk factors present in childhood is emerging. However, in this section, we focus on some of the biggest risk factors for osteoarthritis, namely obesity, joint injury, and exercise, and consider approaches that provide patients with potentially achievable ways to prevent osteoarthritis (panel).

Weight management

Obesity-related joint damage predates clinical osteoarthritic disease.[142] During the early stages of osteoarthritis, the mechanism for obesity-related joint damage is both meta-inflammatory and biomechanical, with the biomechanical contribution increasing with disease severity, which might explain why weight loss only has a modest effect on knee symptoms and structure in established osteoarthritis, but could be more effective in preventing osteoarthritis.[61] Adults gain weight at around 0·5–1 kg per year from early to mid-adulthood,[143–145] and in transitional life stages such as pregnancy.[146] Recent National Health and Nutrition Examination Survey data showed that in 13 802 adults from the USA (age 36–79 years), on average women gained 5·4 kg and men 2·6 kg over 10 years.[147] Low intensity weight-related behaviour interventions for small energy deficits, estimated to be around 30 kilojoules per day or 7 kcal, or 4% of total energy expenditure, can prevent weight accumulation.[148] Such low intensity lifestyle programmes have been shown to reduce knee pain in community populations not selected for osteoarthritis[149] and it is estimated that slowing this weight gain from early adulthood to around age 65 years could save considerable health-care costs by reducing the need for knee replacements.[150] As we target obesity to prevent osteoarthritis (in addition to focusing on weight loss),

targeting this slow weight gain is important and potentially more achievable than targeting weight loss once the weight has accumulated.

Injury

Prevention of injury is important across all joints. In the knee, osteoarthritis risk increases 4–6-fold after injury.[14] There is no evidence that anterior cruciate ligament reconstruction or partial meniscectomy reduce the risk of long-term osteoarthritis, although there might be some short-term (<6 months) improvement in symptoms.[151–153] A recent systematic review found that measures using specific training interventions are cost effective, particularly for prevention of ankle, hamstring, and anterior cruciate ligament injuries.[154]

Maintaining activity

There is no current evidence that a specific type and amount of exercise is best for prevention of osteoarthritis. However, maintaining activity is important to maintain a healthy joint[155] and the integrity of surrounding joint structures, such as muscle, ligaments, bone, and cartilage. For lower limb joints, there is evidence that physical inactivity results in rapid reduction in muscle size and strength,[155] reduced bone integrity, and the amount of knee cartilage. Walking should be encouraged as a low cost, accessible, and acceptable form of activity for most people to help prevent osteoarthritis. For those who enjoy running, there is no evidence that it causes osteoarthritis.[156]

Contributors

All authors contributed to the design of the manuscript, wrote the manuscript, and approved the final version.

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