Osteoarthritis

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Osteoarthritis is a leading cause of disability and source of societal cost in older adults. With an ageing and increasingly obese population, this syndrome is becoming even more prevalent than in previous decades. In recent years, we have gained important insights into the cause and pathogenesis of pain in osteoarthritis. The diagnosis of osteoarthritis is clinically based despite the widespread overuse of imaging methods. Management should be tailored to the presenting individual and focus on core treatments, including self-management and education, exercise, and weight loss as relevant. Surgery should be reserved for those that have not responded appropriately to less invasive methods. Prevention and disease modification are areas being targeted by various research endeavours, which have indicated great potential thus far. This narrative Seminar provides an update on the pathogenesis, diagnosis, management, and future research on osteoarthritis for a clinical audience.

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Introduction

Osteoarthritis is a common and disabling condition that represents a substantial and increasing health burden with notable implications for the individuals affected, health-care systems, and wider socioeconomic costs.[1,2] With the combined effects of ageing and increasing obesity in the global population, along with increasing numbers of joint injuries, this already burdensome syndrome is becoming more prevalent, with worldwide estimates suggesting that 250 million people are currently affected.

In this context of substantive burden, the majority of patients with osteoarthritis do not receive appropriate management therapies.[3] Osteoarthritis is a complex chronic disease, frequently compounded by the presence of multimorbidity. Typical management is best characterised as palliative and reactive, rather than focused on shared decision making or coordinated and proactive and preventive actions. However, considering the increasing individual and societal burden of osteoarthritis, the approach towards management should change towards individualised patient care that is based on their specific needs, which could be achieved through a biopsychosocial and medical framework.[4]

The overview we present here is timely given recent changes in conceptions of osteoarthritis pathogenesis and pain aetiology, and as such, the newly apparent inappropriate management, which needs redressing. Osteoarthritis is a disease of the whole joint, involving structural alterations in the articular cartilage, subchondral bone, ligaments, capsule, synovial membrane, and periarticular muscles.[5] Pain is the dominant symptom and is a major driver of clinical decision making and health service use, and is best framed within a biopsychosocial model.[6] Surgery should be reserved for cases in which all appropriate, less invasive options that have been delivered for a reasonable period have not provided adequate symptom relief. These topics are the focus of this narrative Seminar, along with recent promising research on prevention and disease modification.

Search strategy and selection criteria

We searched PubMed with the search term "osteoarthritis" in combination with the terms "incidence"; "prevalence"; "burden"; "economic"; "costs"; "comorbidity"; "mortality"; "pain mechanisms"; "etiology"; "diagnosis"; "guidelines"; "recommendation"; "management"; "surgery", "replacement", or "arthroplasty"; "disease modification"; and "prevention". We focused on publications from the past 5 years (Jan 31, 2014, to Jan 31, 2019), published in English on meta-analyses or systematic reviews, and on hip and knee osteoarthritis, but did not exclude other articles.

Key messages

- Global prevalence of osteoarthritis is increasing and the burden of the disease will rise
- Osteoarthritis will become one of the most prevalent diseases in populations from high-income countries in the coming decades
- Imaging is not needed to diagnose osteoarthritis
- Key treatments are education, exercise, and weight loss if needed
- Because of the heterogeneity of the disease and comorbidities involved, personalised treatment is essential
- Disease-modifying treatment is not yet available
- Pain-modifying treatment, especially which treats or prevents sensitised pain, is essential in the coming years
- Inappropriate treatments including arthroscopy and opioids should be actively discouraged
- Careful selection of appropriate candidates for surgical referral and joint replacement would optimise outcomes
- Prevention of osteoarthritis is in its infancy, but lifestyle interventions seem promising

Epidemiology and burden

Prevalence

Clinically, the knee is the most common site of osteoarthritis, followed by the hand and hip.[1,7,8] A systematic review[9] showed that the reported prevalence of osteoarthritis in individual studies depended on the definition of osteoarthritis used, as well as on the age categories,

countries of origin, and sex distribution of the study population. In table 1, we show the prevalence data according to these variables for the population-based studies (not the hospital-based) used in that review. Overall, the data indicated much higher prevalence for radiographic osteoarthritis than for symptomatic osteoarthritis, and for knee and hand osteoarthritis than for hip osteoarthritis. Furthermore, knee or hand osteoarthritis was more prevalent in women than in men, especially symptomatic osteoarthritis. Of note was the low prevalence of hip osteoarthritis in Asian countries.

A Swedish registry data study (of primary care and secondary care data)[7] counted the proportion of people aged 45 years and older with any form of doctor-diagnosed osteoarthritis (knee, hip, hand, or other locations except the spine), which was 26·6% for the Skåne region in the southern part of Sweden in 2012. Of the prevalent cases, 141 313 (26·8%) of 531 254 were cases of osteoarthritis in multiple joints. By 2032, the proportion of the population aged 45 years and older with doctor-diagnosed osteoarthritis is estimated to increase from 26·6% to 29·5% for any location, from 13·8% to 15·7% for the knee, and from 5·8 to 6·9% for the hip.[7] The Dutch population prevalence of doctor-diagnosed osteoarthritis (hip, knee, hand, or feet) is estimated to increase from 7% in 2011, to 12% in 2040.[10]

Incidence

Spanish and UK general practice registry data have been used to report on the incidence of osteoarthritis in the general population,[1,11] and showed that the effects of age on individual risk of hip, hand, and knee osteoarthritis in women follow similar patterns, with risk for knee and hand increasing rapidly (much more rapidly than in men) between the ages of 50 years and 75 years (figure 1).[1] Both studies reported peaks in incidence generally around the age of 75 years (prevelance of 4–5% for hand OA, 6% for hip OA, and 16–17% for knee OA).[1,11]

	Studies (n)	Age of the study population (years)	Prevalence in women (%)	Prevalence in men (%)
Knee				
Radiographic				
Adults				
Europe	1	≥22 years	14%	12%
Asia	2	≥24 years and 40–75 years	31% and 61%	23% and 53%
North America	3	≥20 years, ≥20 years, and 42–52 years*	29%, 50%, and 14%*	32% and 44%
Middle-aged and older population				
Europe	2	≥45 years and ≥55 years	10% and 29%,	4% and 16%,
Asia	3	≥50 years, ≥50 years, and ≥54 years	30%, 61%, and 30%	10%, 46%, and 16%
North America	1	≥45 years	31%	24%
Oceania	2	≥45 years* and ≥51 years	22%* and 70%	65%
Older population				
Asia	6	≥60 years, ≥60 years, ≥62 years, ≥65 years, ≥65 years, and ≥63 years*	43%, 79%, 47%, 37%, 54%, and 47%*	22%, 58%, 41%, 18%, and 17%
North America	2	≥60 years and ≥63 years*	42% and 35%*	31%
Symptomatic				
Adults				
Europe	1	≥19 years	9%	3%
Asia	1	35–64 years	15%	7%
Middle-aged and older population				
Europe	1	≥50 years	23%	8%
Asia	3	≥50 years, ≥50 years, and ≥54 years	14%, 38%, and 20%	7%, 7%, and 9%
North America	1	≥45 years	19%	14%
Older population				
Europe	1	≥60 years	15%	9%
Asia	3	≥60 years, ≥62 years, and ≥65 years	15%, 10%, and 27%	6%, 4%, and 11%
North America	1	≥60 years	14%	10%
Self-reported				
Adults				
Europe	5	≥18 years, ≥20 years, ≥25 years, ≥25 years, and 24–64 years	14%, 14%, 14%, 16%, and 8%	6%, 6%, 10%, 13%, and 6%
Asia	1	≥15 years	10%	7%

(Table 1 continues on next page)

	Studies (n)	Age of the study population (years)	Prevalence in women (%)	Prevalence in men (%)
(Continued from previous page)				
Hip				
Radiographic				
Adults				
Europe	2	≥20 years and ≥23 years	7% and 5%	7% and 11%
Middle-aged and older population				
Europe	2	≥45 years and ≥55 years	19% and 16%	27% and 14%
Oceania	1	≥51 years	47%	43%
Older population				
Europe	1	≥60 years	5%	11%
Asia	2	≥60 years and ≥60 years	0% and 1%	2% and 1%
Symptomatic				
Adults				
Europe	1	≥19 years	2%	0%
Older population				
Europe	1	≥60 years	8%	7%
Self-reported				
Adults				
Europe	4	≥18 years, 24–75 years, ≥25 years, and ≥25 years	7%, 6%, 10%, and 12%	2%, 5%, 4%, and 7%
Hand				
Radiographic				
Adults				
Europe	1	≥30 years	48%	44%
Asia	2	40–75 years and ≥40 years*	36% and 74%*	30%
North America	2	≥40 years and 42–52 years*	41% and 21%*	42%
Middle-aged and older population				
Europe	1	≥50 years	67%	55%
Oceania	1	≥45 years*	45%*	..
Older population				
Asia	1	≥60 years	47%	45%
Symptomatic				
Adults				
Europe	1	≥19 years	3%	<1%
Older population				
Asia	1	≥60 years	6%	3%
North America	1	≥71 years	26%	13%
Self-reported				
Adults				
Europe	2	≥20 years and 24–76 years	10% and 6%	2% and 3%

*Female-only population.

Table 1: **Prevalence of knee, hip, and hand osteoarthritis with continent, sex, and age stratification according to population-based studies[9]**

Burden of disease

Knee osteoarthritis accounts for approximately 85% of the burden of osteoarthritis worldwide.[12] In terms of disability burden, osteoarthritis and diabetes were responsible for the largest increases in years lived with disability at the global population level, relative to the other top 20 causes of disability, when comparing the period 1990–2005 with 2005–15; attributable to the global ageing population and obesity epidemic.[12] Osteoarthritis accounted for 3·9% of years lived with disability worldwide in 2015, and by 2020 it is expected to be the fourth leading cause of years lived with disability globally.[13]

Costs of disease

The medical cost of osteoarthritis in various high-income countries has been estimated to account for between 1% and 2·5% of the gross domestic product of these countries,[14] with hip and knee joint replacements representing the major proportion of these health-care costs. Although appropriate attention is given to direct

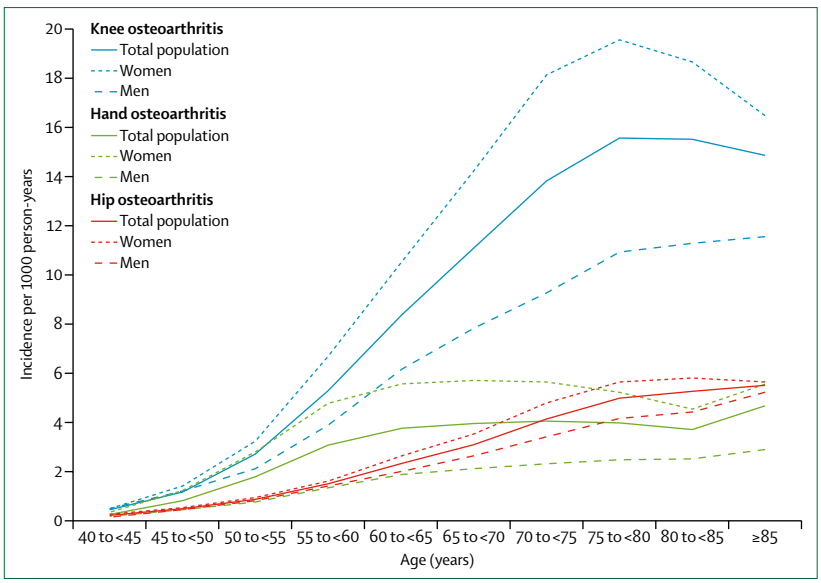

Figure 1: **Osteoarthritis incidence**
Age-specific and gender-specific incidence (per 1000 person-years) of knee osteoarthritis (blue), hand osteoarthritis (green), and hip osteoarthritis (red).[1] These data are representative of the general population from Catalonia (Spain).

health-care costs, the indirect costs due to work loss and premature retirement are also substantial and often ignored in considering disease burden.[15] The national costs, together with the personal costs for patients with osteoarthritis, such as loss of income and the subsequent reductions in personal savings, greatly surpass the direct health-care costs.[16,17]

Risk factors

Age is one of the most evident risk factors for osteoarthritis. The increasing incidence of osteoarthritis with age is a result of cumulative exposure to various risk factors and biological age-related changes in the joint structures.[18]

For knee osteoarthritis, strong evidence indicates a variety of moderate to strong risk factors, including female sex, obesity, and previous knee injury.[19] Knee malalignment is also a moderate to strong risk factor,[20,21] and knee extensor muscle weakness is likely to be a weak risk factor.[22]

For hip osteoarthritis, risk factors such as female sex and obesity are less pronounced, but hip deformities such as cam deformity or acetabular dysplasia moderately to strongly increase risk.[23] Cam deformity and mild dysplasia increase the risk of osteoarthritis especially in the middle-aged (55–65 years), but not in the older population (65 years and older),[24] whereas severe dysplasia is strongly associated with hip osteoarthritis and leads to its development at an early age (less than 50 years).[25]

Heavy work activities are risk factors for both hip and knee osteoarthritis; employment in farming or the construction industry is especially associated with hip osteoarthritis,[26] and work that involves frequent kneeling and heavy lifting is associated with knee osteoarthritis.[27]

Several high-impact sports (eg, football, handball, hockey, wrestling, weight-lifting, and long-distance running) have been reported as moderately to strongly associated with an increased risk of hip osteoarthritis[28] or knee osteoarthritis,[29] often with a dose-response dependency. For knee osteoarthritis, the increased risk with sport is partly because of knee injuries; for hip osteoarthritis, the risk might be associated with the presence of cam impingement, which can develop during sporting activities in adolescents.[30]

The contribution of genetics in osteoarthritis is estimated to be between 40% and 80%, with a stronger genetic contribution in hand and hip osteoarthritis than for knee osteoarthritis.[31] Rare mutations in monogenetic disorders associated with osteoarthritis have a large effect, resulting in early-onset osteoarthritis. In contrast, late-onset osteoarthritis is often multifactorial and caused by many common DNA variants together with other risk factors. The effect size of these common variants is generally small.[31]

Comorbidity outcomes

In general, the available studies so far indicate an association between osteoarthritis and atherosclerosis-related disease.[32] Meta-analyses show a small increased risk of cardiovascular disease development among patients with osteoarthritis compared with individuals who do not have osteoarthritis.[33,34] Additionally, the presence of osteoarthritis was found to result in a slightly increased risk of cardiovascular death in patients compared with individuals who do not have osteoarthritis.[34,35] A large study in 2017 showed that the small increase in risk of stroke in patients with osteoarthritis compared with individuals who do not have osteoarthritis was independent of non-steroidal anti-inflammatory drug (NSAID) use.[36] Some common pathways for osteoarthritis and cardiovascular disease, such as fat metabolism and the innate immune system, have also been suggested.[32]

Many patients with osteoarthritis, older patients (65 years and older) in particular, will have one or more comorbidities. A summary of four Australian studies showed that over half of the older patients with arthritis had hypertension, followed by cardiovascular disease (20%), dyslipidaemia (19%), diabetes (14%), and mental health disorders including depression (12%).[37]

Meta-analyses show that one or more of such comorbidities or other chronic diseases, such as diabetes or cardiovascular disease, are predictive of faster worsening of pain, or of faster deterioration.[38]

New insights on pathogenesis

Osteoarthritis is a whole joint disease, involving structural alterations in the hyaline articular cartilage, subchondral bone, ligaments, capsule, synovium, and periarticular muscles.[5,39] The complex pathogenesis of osteoarthritis involves mechanical, inflammatory, and metabolic factors, which ultimately lead to structural destruction and failure

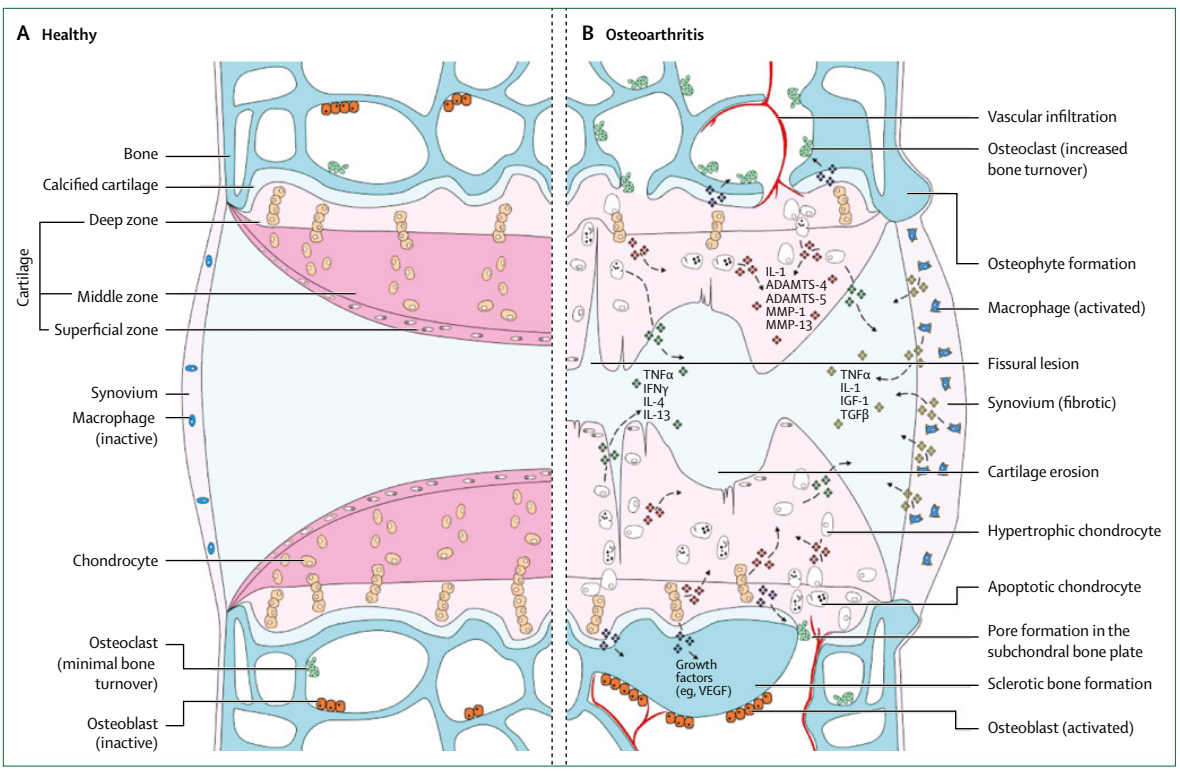

Figure 2: **Signalling pathways and structural changes in the development of osteoarthritis**
ADAMTS=a disintegrin and metalloproteinase with thrombospondin-like motifs. IL=interleukin. MMP=matrix metalloproteinase. TNF=tumour necrosis factor. IFN=interferon. IGF=insulin-like growth factor. TGF=transforming growth factor. VEGF=vascular endothelial growth factor. Reproduced from Glyn-Jones et al.[44]

of the synovial joint. The disease is an active dynamic alteration arising from an imbalance between the repair and destruction of joint tissues, and not a passive degenerative disease or so-called wear-and-tear disease as commonly described.[40,41]

During the osteoarthritis process, cartilage composition changes and the cartilage loses its integrity.[42] The compositional changes alter the cartilage material properties and increase its susceptibility to disruption by physical forces. Initially, erosions are only at the surface; then later more deep cartilage fissures are followed by the expansion of the calcified cartilage zone. In an attempt at repair, the hypertrophic chondrocytes exhibit increased synthetic activity, but in doing so generate matrix degradation products and proinflammatory mediators that deregulate chondrocyte function and act on the adjacent synovium to stimulate proliferative and pro-inflammatory responses. Proliferating synoviocytes also release proinflammatory products; this process is accompanied by tissue hypertrophy and increased vascularity. In the subchondral bone, bone turnover is increased, and vascular invasion takes place, going from the subchondral bone, through the tidemark, and into the cartilage. This bone remodelling and repair is also associated with the development of subchondral bone marrow lesions. The osteophytes that develop at the joint margins through reactivation of endochondral ossification are strongly affected by inflammatory biological factors, but also by overload and abnormal joint kinematics.[43] Figure 2 summarises the pathogenic process in detail.

Osteoarthritis is typically described as a heterogeneous disease with a wide range of underlying pathways, which lead to similar outcomes of joint destruction.[45] In this context, osteoarthritis can be considered as a syndrome rather than a single disease. Each of the common osteoarthritis risk factors might instigate a different mechanistic pathway leading to osteoarthritis, such that the mediators that promote the development of osteoarthritis in older adults might be different from those that promote osteoarthritis after a joint injury in a younger adult or in obese individuals. A number of stratifications have been proposed on the basis of specific pathological processes to classify different mechanistic subgroups, which include an increased inflammatory component,[46] mechanical overload,[47] metabolic alterations,[48] and cell senescence.[49] These mechanistic phenotypes probably overlap and warrant further validation.

Causes of osteoarthritis pain

Patients with osteoarthritis experience pain as the most disabling symptom. Pain is a major driver of clinical decision making and health service use, and is best framed within a biopsychosocial model (figure 3).[6] Morning stiffness, reduced range of motion, crepitus,

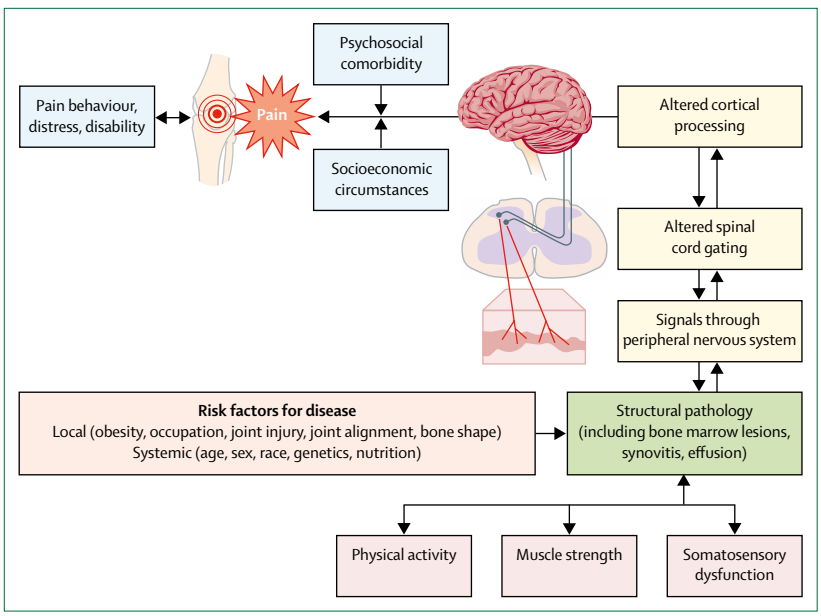

Figure 3: **The cause of pain in osteoarthritis within a biopsychosocial model**

joint instability (buckling or giving-way), swelling, muscle weakness, fatigue, and pain-related psychological distress are also seen frequently in patients with osteoarthritis.[50]

The pain in knee osteoarthritis is typically an intermittent and mainly weight-bearing (mechanical) pain. Often, the intermittent pain is predictable, but when it becomes more severe, more frequent, or unpredictable, patients more often categorise their pain as unacceptable.[51] The concept and understanding of so-called flare-ups in osteoarthritis are developing, which is now considered broader than just an exacerbation of pain.[52,53]

Traditional imaging with x-ray only shows moderate associations between structural osteoarthritis and the presence of pain in affected individuals.[54] Structural osteoarthritis assessed with MRI shows similar moderate associations with the presence of joint pain.[55] The association between structural osteoarthritis on x-ray and pain becomes much more evident if looking at frequent pain rather than infrequent pain,[56,57] at more severe structural osteoarthritis rather than less severe cases,[56] or at pain discordant knees within a patient.[56] Furthermore, MRI has indicated that the presence and severity of pain are associated with specific features of osteoarthritis, such as bone marrow lesions and synovitis,[57] and that an increase or decrease in pain within a person correlates with a change in synovitis or in the size or number of bone marrow lesions.[58]

Pain mechanisms

Apart from peripheral nociceptive pain mechanisms (including increased responsiveness of peripheral nociceptors by ongoing tissue injury or inflammation in the joint), pain sensitisation by means of neuropathic pain mechanisms or central pain mechanisms seem to be present in a large proportion of patients with osteoarthritis.[41,43] Neuropathic pain arises from structural changes in joint innervation or from nerve changes in the peripheral nervous system or spinal cord.[59] Central pain mechanisms include enhanced activity of descending pain facilitation pathways and loss of descending antinociceptive pathways.[60]

A meta-analysis[61] of pain sensitisation in patients with osteoarthritis, measured objectively by quantitative sensory testing (QST), showed that pain pressure thresholds (at the affected site but also remote sites), temporal summation, flexor withdrawal responses, and conditioned pain modulation differed between the patients and healthy controls. This meta-analysis also showed that in patients with knee osteoarthritis with high symptom severity, pressure pain thresholds were lower than in patients with low symptom severity (corrected mean effect size 0·51).[61]

From self-reported neuropathic pain screening questionnaires like the (modified) painDETECT, a meta-analysis in 2017[62] estimated that 23% of patients with osteoarthritis were likely to have a form of neuropathic pain. Several other studies showed that central pain mechanisms (as detected by QST) were present in the people that were defined as having neuropathic pain, as assessed with the (modified) painDETECT.[63,64] Pain sensitisation has been shown to be independent of radiographic severity or symptom or disease duration, but synovitis and effusion seem to be related to pain sensitisation.[65,66]

The diagnosis of osteoarthritis and the role of imaging

Clinical diagnosis is the standard for confirming osteoarthritis, made on the basis of symptoms (pain, brief morning stiffness, and functional limitations) and a brief physical examination (crepitus, restricted or painful movement, joint tenderness, and bony enlargement). Appropriate use of diagnostic criteria (such as those from the American College of Rheumatology or the European League Against Rheumatism for knee osteoarthritis; figure 4) is recommended,[67,68] although the need for early osteoarthritis criteria has been stressed to identify patients in an early stage of the disease, to allow for key treatment from the earliest symptoms. Pain symptoms such as pain during stair use in combination with crepitus or joint line tenderness might form such criteria, but these symptoms need further validation.[69] Plain radiographs are not needed for diagnosis, but like laboratory tests can be considered if the presentation is atypical or if other diagnoses are strongly suspected.[70] Initial assessment should include a complete history and physical examination, identifying the effect of osteoarthritis on function, quality of life, mood, social participation and relationships, occupation, leisure activities and sleep,[71] and identifying relevant comorbidities. This holistic assessment engenders a patient–professional partnership and collaborative care to facilitate shared decision making, to ultimately improve outcomes.[72] Patient preferences and beliefs surrounding certain therapies

are important to consider as adherence to therapeutic recommendations can otherwise be compromised. Patient knowledge of the disease, treatment alternatives, and previous experiences and expectations of treatment should also be ascertained. All of this information should be used to develop an appropriately tailored management plan informed by patient expectations, preferences, and goals, and existing evidence.

Management

Overall, the key management strategies for knee and hip osteoarthritis are in broad agreement across the guidelines of the various stakeholder organisations,[73,74] which include large professional societies, research societies, and governmental organisations.

Key treatment strategies

In the guidelines, non-pharmacological methods such as education and self-management, exercise, weight loss if overweight or obese, and walking aids as indicated, are widely recommended and seen as first-line treatment.[73,74] Experts and patients have reached consensus on multiple aspects that are important in the education of patients, such as information about the different treatment approaches (eg, the importance of regular physical activity, individualised exercise, and to lose weight if overweight, but also about surgery—eg, "your osteoarthritis symptoms can often be eased significantly without requiring an operation"), information about the disease (eg, "osteoarthritis is not an inevitable part of getting older"), about the pathophysiology, and about the diagnostic imaging (eg, "joint damage on an x-ray does not indicate how much your osteoarthritis will affect you").[75]

Exercise therapy is particularly helpful in decreasing pain and improving joint motion, for which high-quality evidence has been available in the past decade,[76,77] with estimated effect sizes of 0·4–0·5 for hip osteoarthritis and knee osteoarthritis. Exercise therapy (consisting of strengthening exercise and general aerobic exercise) is now seen as one of the key elements of osteoarthritis management, although the challenge is to get this therapy widely implemented and to enhance long-term adherence. In a systematic review,[78] several modifiable barriers and facilitators to intentional exercise have been identified, related to the circumstances of a person's situation or environment that either discourage or encourage the development of exercise skills and abilities, independence, social competence, and adaptive behavior. Negative beliefs about the consequences of exercise are also barriers.[78]

For weight loss interventions in patients who are overweight or obese, evidence is only available for knee osteoarthritis, with an effect size of 0·37,[79] but not for hip osteoarthritis. Several trials clearly indicate a dose-response association between the amount of weight loss and the effect on pain and function.[80–83] The Arthritis, Diet and Activity Promotion and Intensive Diet and Exercise for Arthritis trials[80,81] showed that the combination of dietary weight management and exercise yield better effects on pain and function than either diet or exercise alone. The challenge for this intervention is the maintenance of weight loss in the long term.

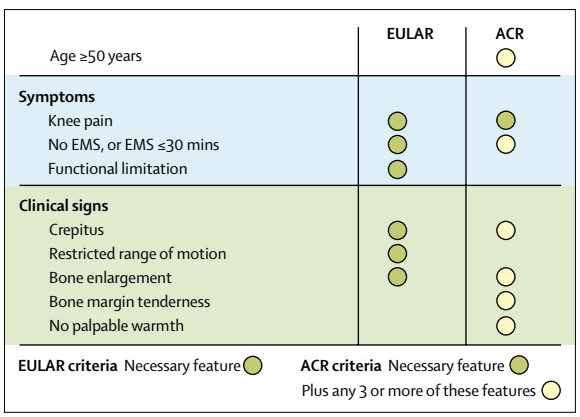

***Figure 4*: EULAR and ACR criteria for knee osteoarthritis**
Shown are the ACR clinical classification criteria for osteoarthritis of the knee,[67] and the EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis.[68] In developing the EULAR guidelines, the estimated probability of having radiographic knee osteoarthritis increased with increasing number of positive features, to 99% when the six indicated symptoms and signs (green dot) were present (when assuming a 12·5% background prevalence of knee osteoarthritis in adults aged ≥45 years). EULAR=European League Against Rheumatism. ACR=American College of Rheumatology. EMS=early morning stiffness.

Pain medication

Pharmacological methods most often recommended in the guidelines include paracetamol and NSAIDs.[73] Paracetamol was historically the first-line pain medication for osteoarthritis; however, in 2017 a meta-analysis[84] concluded that given the very small effect sizes of paracetemol (less than 0·2) compared with placebo, along with safety concerns, it is of little use as a single agent for the treatment of osteoarthritis. Other first-line methods such as topical NSAIDs were shown to be effective for pain relief in osteoarthritis compared with placebo in a 2018 meta-analysis, with (corrected) mean effect sizes of 0·30 for pain relief and 0·35 for function.[85] For topical NSAIDs, so far no serious gastrointestinal or renal adverse events have been observed in trials or in the general population.[85]

Oral NSAIDs have been shown to be effective in terms of clinically relevant improvement of both pain and function, for which the effect sizes in the available studies vary across different NSAIDs and doses.[84] However, safety (particularly relating to gastrointestinal and cardiovascular events) is an important consideration in selecting the preparation and dose for individual patients, and the use of oral NSAIDs is preferably restricted to short-term use (as needed) at the smallest dose possible.

Intra-articular corticosteroids are recommended for hip and knee osteoarthritis for patients who have not responded to oral or topical analgesics.[73] However, the most recent Cochrane review in 2015[86] concluded that the

evidence for clinically important benefits of intra-articular corticosteroids for knee osteoarthritis at up to 6 weeks ([corrected] mean effect size 0·41) remains unclear in view of the overall low quality of trials. An individual patient data (IPD) meta-analysis provided clear evidence that patients with more severe pain responded much better to intra-articular corticosteroid injections than those with less pain and compared with placebo. The results also indicated, although only of borderline significance, that people with signs of joint inflammation responded better than those without signs of such inflammation compared with placebo.[87] Controversy surrounding this treatment has been raised after a randomised study in 2017 indicated that a 3-monthly intra-articular injection with corticosteroids in patients with knee osteoarthritis resulted in slightly more loss of cartilage volume over 2 years than did the placebo treatment;[88] however, whether such slight differences have an effect on long-term clinical outcomes is unknown.

Duloxetine, mentioned in some guidelines to consider for refractory pain, is a serotonin and norepinephrine reuptake inhibitor with antidepressant, central pain inhibitory, and anxiolytic activities.[74,89] For knee osteoarthritis, a meta-analysis of three trials[89] suggested that duloxetine compared with a placebo control resulted in a clinically relevant reduction in symptoms, and had acceptable adverse effects for the type of treatment after about 3 months of treatment. Since 2017, two large trials in China[90] and Japan[91] have added to the evidence that duloxetine reduces pain and improves function. Whether this kind of intervention is especially effective in patients with neuropathic or central pain involvement needs further investigation.

A meta-analysis showed that tramadol or tramadol plus paracetamol produces symptom relief, and improves function in patients with osteoarthritis, but that these benefits are small.[92] For non-tramadol opiates, a 2014 meta-analysis showed that the small mean benefit of these drugs occurs with significant increases in the risk of adverse events; for the pain outcome in particular, observed effects (mean effect size for pain relief 0·28) were of questionable clinical relevance.[93] Direct comparisons between opiates and non-opiates for the relief of osteoarthritis pain or lower back pain showed a greater effect with non-opiates, and more side-effects from opiates.[94] Although most guidelines were uncertain about the use of opiates until 2014,[73,74] more recently, the small gain weighted against the side-effects, and the risk of addiction and overdosage, has led to an overall discouragement of prescribing these products to patients with osteoarthritis.[95–98]

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Other treatments

Controversy in the guidelines remains about the use of knee braces and heel wedges, and acupuncture, intra-articular hyaluronans, and glucosamine or chondroitin are typically not recommended.[73,74] In meta-analyses of intra-articular hyaluronans compared with saline injections, the larger and high quality studies (masked outcome assessment) compared with the smaller and non-masked studies showed effect sizes of insufficient clinical relevance.[98–100] That high quality and larger studies show low efficacy also seems to be the case for chondroitin[101,102] and glucosamine[101,103] compared with placebo, even for the most effective (strongest potency) crystalline glucosamine sulphate product.[103] Acupuncture is likely to have little or no effect in reducing pain compared with sham treatment.[104–106] For wedged insoles, the evidence is scarce and conflicting,[107] but the only large high-quality study for this intervention[108] did not find a significant effect on pain or function of wedged insoles compared with neutral insoles. Meta-analyses on valgus bracing for medial compartment knee osteoarthritis suggest some improvement in pain, but the quality of the evidence is low.[107,109]

New pain treatments

Several new pain treatments are in development. For almost a decade, nerve growth factor (NGF) antibodies have been tested and yielded promising results with respect to pain reduction in patients with hip and knee osteoarthritis. Chen and colleagues[110] did a meta-analysis of ten studies that compared tanezumab (a humanised monoclonal antibody against NGF) with placebo. Tanezumab was statistically superior to placebo, but borderline clinically relevant, and these effects were not dose-dependent. Two other studies in the analysis showed that tanezumab was significantly superior to active treatments like NSAIDs or opiates (oxycodone). Safety concerns put the clinical trials on hold in 2010. The trials were resumed in 2015 with restricted dosages (5 mg) and restricted co-intervention with NSAIDs,[111] to limit the serious side-effect of rapidly progressive osteoarthritis.

Personalised treatment

Given the small to moderate effect size of symptomatic treatments in osteoarthritis and the heterogeneity of patients, several sets of osteoarthritis guidelines have addressed the need for research on clinical predictors of response to the different treatments. The OA Trial Bank brings together IPD from published randomised controlled trials for solid subgroup IPD meta-analyses. Two meta-analyses have been published since 2016: one identified a subgroup with severe pain especially responsive to intra-articular corticosteroid,[87] whereas the other could not identify any subgroup that was more responsive to an intervention with glucosamine.[112] Several more of these subgroup meta-analyses of IPD for other interventions are underway.[113–115]

When to refer for surgery and which surgical options to use

Joint replacement surgery

Joint replacement surgery is a clinically relevant and cost-effective treatment for end-stage osteoarthritis.[116,117]

Joint replacement, however, can only be considered cost-effective if the procedure is restricted to patients with more severely affected functional status.[118] The lifetime risk of undergoing total joint replacement is substantially less than the risk of developing symptomatic hip or knee osteoarthritis; the mortality-adjusted lifetime risk of total hip replacement at age 50 years has been estimated at 11·6% for women and 7·1% for men, and for knee replacement, 10·8% for women and 8·1% for men.[119]

Referral of patients with end-stage osteoarthritis to a surgeon should be considered if all appropriate conservative options, delivered for 6 months, have been unsuccessful. Furthermore, the decision to refer to an orthopaedic surgeon should be made if patient quality of life is greatly reduced because of end-stage osteoarthritis. For instance, the characteristics of end-stage osteoarthritis include joint pain, which disrupts normal sleep patterns and causes a severe reduction in capable walking distance and marked restriction of daily activities.[119]

Outcomes from total joint replacement can be optimised if patient selection identifies marked joint space narrowing. Most improvement will be made in patients with complete joint space loss and evident bone attrition.[120,121] Up to 25% of patients presenting for total joint replacement continue to complain of pain and disability 1 year after well performed surgery.[122,123] Careful preoperative patient selection (including consideration of the poor outcomes that are more common in people who are depressed, have minimal radiographic disease, have minimal pain, and who are morbidly obese), shared decision making about surgery, and informing patients about realistic outcomes of surgery are needed to minimise the likelihood of dissatisfaction.[124] The randomised trial in 2015 that compared total knee replacement with non-surgical treatment in patients with knee osteoarthritis showed that the total knee replacement group had greater pain relief and functional improvement after 12 months than the non-surgical group.[125] However, total knee replacement was associated with more serious adverse events than non-surgical treatment, and most patients in the non-surgical group did not undergo total knee replacement before the 12-month follow-up.

Complications associated with joint replacement include those in common with other surgeries (eg, venous thromboembolism and surgical site infection) as well as complications specific to operations involving joints, such as neurovascular injury, prosthetic joint infection, peri-implant fractures, and issues related to wear and tear of the prosthesis.[126]

Knee osteotomy

Knee osteotomy has been shown to have benefits for pain and function, although randomised comparisons with non-surgical treatments are unavailable at present.[127] Its use is restricted for people with unicompartmental knee osteoarthritis (often varus malaligned) as the procedure induces a load transfer from the diseased compartment to the healthy compartment. Osteotomy is mainly considered for young and active patients with osteoarthritis of moderate radiographic severity, and can postpone joint replacement surgery for up to 10 years in more than 85% of patients.[128] An alternative surgical option for patients with unicompartmental knee osteoarthritis is a unicompartmental knee prosthesis. Overall, high tibial knee osteotomy allows improved activity for younger patients, whereas unicompartmental knee prosthesis is more suitable for older patients because of the shorter rehabilitation time and faster recovery period.[129] Unicompartmental knee prosthesis also has significantly less morbidity (eg, length of hospital stay, and compilations like tromboembolism, myocardial infarction, and stroke) and mortality than total knee prostheses, but somewhat higher failure (ie, worse implant survival) rates as reported in national joint registries.[130]

Knee joint distraction

Another knee-preserving treatment that has been studied in recent years is knee joint distraction, which comprises of 6–8 weeks of joint distraction with an external fixator;[131,132] however, single or multiple pin track infections have been found to occur frequently (in 60% of the treated patients).[131,132]

Arthroscopic knee surgery

Arthroscopic knee surgery, the most common elective orthopaedic procedure, continues to be widely used for the management of knee osteoarthritis, despite no rigorous evidence of efficacy.[133–136] Notably, several studies[133–136] have shown that knee arthroscopy has minimal benefit, if any, and a clear risk of harm compared with sham surgery or less invasive treatments for knee osteoarthritis or degenerative meniscal tears. Arthroscopic partial meniscectomy still has a role in people with clear evidence of mechanical knee locking (objectively unable to fully extend the knee), although procedural numbers suggest that this procedure is widely used in other patient groups.

Considering that arthroscopic knee surgery has an undeniably large placebo effect, it could be justified were it not for its substantial costs and potential harms. However, meniscectomy (partial or full) can increase the speed of progression of osteoarthritis,[137,138] and the most common serious adverse outcomes following elective arthroscopy include deep venous thrombosis (579 [0·32%] of 180 717), effusion and synovitis (154 [0·09%]), pulmonary embolus (147 [0·08%]), and haemarthrosis (134 [0·07%]).[139] Additionally, arthroscopy increases the risk of and shortens the time to joint replacement.[140,141] This evidence against the use of arthroscopy for knee osteoarthritis is reflected in guidelines, including those of the American Academy of Orthopaedic Surgeons.[142] The persisting high frequency of this procedure represents an important gap in evidence-based practice.

Disease modification

Current pharmacological approaches for the management of osteoarthritis are largely palliative. To mitigate the epidemic of osteoarthritis, modifying its structural progression and symptomatic consequences in tandem has become a focus of drug development.[143] Drugs with such capacities are referred to as disease-modifying osteoarthritis drugs and can potentially cause retardation (slowing of the speed of disease progression), a complete halt in disease progression, or a reversal in disease progression (regeneration of the target tissue). At present, despite many trials, no drugs have garnered regulatory approval for this indication.

Therapeutic development has been constrained by several factors, including regulatory hurdles, the slow progression of osteoarthritis, the disease heterogeneity and its multitude of risk factors, the poor association between structural changes and clinically meaningful endpoints, and discord between preclinical and human models limiting translation.[144]

However, many products (table 2) are in late stages of development and show promise; these products are largely more targeted therapies than current palliative drugs and able to be locally administered—specifically via intra-articular injections—which maximises local efficacy while reducing systemic toxicity.[145] Methodological advances in measuring biomarkers, particularly through imaging (eg, detection of reliable, valid quantifiable changes on MRIs), as well as novel trial designs (including methods to diminish placebo responses and post-approval studies that allow increased trial duration to detect longer-term effects on clinical outcomes) will assist in overcoming many of the current technical challenges.

Prevention

Although osteoarthritis is one of the most common diseases, primary prevention is still in its infancy. Some of the risk factors for osteoarthritis are not modifiable and only define a high-risk group; others can either be prevented or modified. Factors that make knee osteoarthritis a high risk and for which overwhelming evidence exists are obesity and previous knee injury.[19] The relevance of a risk factor for prevention can be established by the population attributable fraction (PAF), which depends on both the strength of the risk and the prevalence of the risk factor. A meta-analysis estimated that 5% of new cases of knee osteoarthritis or knee pain were attributed to self-reported previous knee injuries.[19] This PAF might be different for proven meniscal or ligament injury. The evidence suggests that a neuromuscular training programme in high-injury sports can reduce knee injuries by 45–83%.[146] In the long term, such

	ClinialTrials.gov identifier	Company	Structure	Targeted tissue	Mechanism of action	Stage of development
FGF-18						
Sprifermin (AS902330)	NCT01919164	Merck KGaA (Darmstadt, Germany)	Recombinant human FGF-18	Cartilage regeneration and repair	Stimulating chondrogenesis and cartilage matrix production through FGF receptors 2 and 3	Phase 2 (active, not recruiting; estimated to complete in 2019)
PRP						
Human PRP	NCT03491761	NorthShore University HealthSystem (Evanston, IL, USA)	Human PRP from patient whole blood samples	Cartilage regeneration and repair	Directing the local mesenchymal cells to migrate, divide, and increase collagen and matrix synthesis	Phase 2 (recruiting; estimated to complete in 2019)
Gene therapy						
TissueGene-C	NCT03291470 and NCT03203330	TissueGen, Inc (Duncansville, PN, USA)	Allogeneic human chondrocytes modified to express TGF-β1	Cartilage regeneration	Stimulating the regeneration of damaged degenerate cartilage or regrowing lost cartilage	Both phase 3 (not yet recruiting)
Wnt/ß-catenin signalling pathway inhibitors						
SM04690	NCT03122860	Samumed LLC (San Diego, CA, USA)	N-(5-(3-(7-(3-Fluorophenyl)-3H-imidazo(4,5-C)pyridin-2-yl)-1H-indazol-5-yl)-pyridin-3-yl)-3-methylbutanamide	Cartilage catbolism	Induction of protease production, especially matrix metalloproteinases	Phase 2 (completed in early 2018)
PTH						
Teriparatide	NCT03072147	University of Rochester (Rochester, NY, USA)	Recombinant amino-acid fragment (amino acids 1–34) of human PTH	Subchondral bone	Subchondral bone remodelling	Phase 2 (recruiting; estimated to complete in 2021)
MEPE						
TPX-100	NCT03125499	OrthoTrophix (Covina, CA, USA)	A 23-amino acid peptide derived from MEPE	Subchondral bone	Subchondral bone remodelling	Phase 2 (completed in early 2018)
Anti-IL-1						
ABT-981	NCT02087904	AbbVie (Chicago, IL, USA)	A dual variable domain immunoglobulin of IgG1 kappa	Inflammation	Neutralizing IL-1α and IL-1β	Phase 2 (completed in 2016)

FGF=fibroblast growth factor. PRP=platelet-rich plasma. TGF=transforming growth factor. PTH=parathyroid hormone. MEPE=matrix extracellular phosphoglycoprotein. IL=interleukin.

Table 2: **Registered phase 2 and 3 clinical trials on compounds with potential disease-modifying effects**

a programme should also diminish the development of knee osteoarthritis.

The PAF associated with overweight or obesity differs greatly between continents, largely depending on the prevalence of obesity. Meta-analyses in 2011,[147] and 2014,[19] showed that for obesity, the PAF ranged from 8% in China to 50% in the USA; and for overweight, it ranged from 13% in China to 30% in Norway, and in developed countries from 24% to 30%. Indications for the preventive effect of weight reduction are based on observational studies; a seminal study of the Framingham cohort estimated that the reduction in bodyweight from the obese group to the overweight group, and from the overweight group to the normal weight group reduced the incidence of knee osteoarthritis by 21% in men and 33% in women.[148] To date, only one published randomised controlled trial focused on the prevention of knee osteoarthritis, evaluating a diet and exercise programme aimed at reducing bodyweight among middle-aged, overweight women.[149] This study was unable to show a preventive effect of the intervention on knee osteoarthritis development, probably because of low compliance and a limited contrast in weight loss between the intervention and control groups.[149] In post-hoc analyses,[149,150] a 5 kg or 5% weight loss during the first year resulted in a 3·0 times reduction in incident clinical knee osteoarthritis after 6 years (7% incidence in 5 kg or 5% weight loss group *vs* 21% incidence in <5 kg or 5% weight loss group), and a 2·5 times reduction in radiographic knee osteoarthritis development (6% incidence in 5 kg or 5% weight loss group *vs* 16% incidence in <5 kg or 5% weight loss group).[150] More high-quality trials studying the preventive effects of interventions among people at high risk of osteoarthritis are needed.

Overall conclusion and future perspectives

Health-care providers and policy makers should realise that the global population will be confronted with an increase in osteoarthritis in the coming decades, to that degree that it will become one of the most frequent diseases. Although several evidence-based guidelines are available for hip and knee osteoarthritis, the evidence for non-surgical treatment efficacy in hip osteoarthritis compared with in knee osteoarthritis is insufficient, and for other forms of peripheral osteoarthritis it is even scarcer. Osteoarthritis, as a slowly progressive disease with irreversible structural change and in which chronic pain phenotypes can develop, needs early proactive management; however, validated early-stage diagnostic criteria are also unavailable. Furthermore, testing such treatments in early-stage disease, including disease-modifying treatments, probably needs other more sensitive outcomes than the current measures. Our increasing understanding of the importance of different pain phenotypes will need to be matched with tools that can be used in clinical practice to help differentiate these phenotypes. Such stratification will help to indicate the suitability of targeted treatment and (modifiable) risk factors for unfavourable pain phenotypes. Historically, the interest in disease modification has focused on cartilage, which unfortunately has little if any direct association with symptom experience. Insights into the important roles that the synovium (and its inflammation) and bone have in disease pathogenesis and symptom generation have highlighted these tissues as promising targets for future therapeutic advances.

The role of imaging in diagnosing osteoarthritis in clinical practice should be more clearly defined. Although imaging has a limited role in diagnosing osteoarthritis, it has been shown to be an important predictor of success of joint replacement and could therefore have an important role in referral to surgery.

Preventive interventions to date have been limited to weight loss and should be investigated in more depth. Surgical techniques that reduce cam impingement and the different post-knee injury interventions should be assessed for their ability to prevent osteoarthritis. However, because of the long time frame to develop osteoarthritis, intermediate or early outcomes in preventive trials should be identified and validated to make such studies feasible.

Contributors

Both authors contributed equally to conception of the Seminar, to review and appraisal of the literature, and to writing and revision of the manuscript. Both authors confirmed the final version to be published.

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