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(International Society of Orthopaedic Surgery and Traumatology)

Current Concepts in the Management of Osteoarthritis

Module 3

Pain in Osteoarthritis: Causes and New Treatments

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■ Nidhi Sofat, and Anasuya Kuttapitiya

Future directions for the management of pain in osteoarthritis

Abstract: Osteoarthritis (OA) is the predominant form of arthritis worldwide, resulting in a high degree of functional impairment and reduced quality of life owing to chronic pain. To date, there are no treatments that are known to modify disease progression of OA in the long term. Current treatments are largely based on the modulation of pain, including NSAIDs, opiates and, more recently, centrally acting pharmacotherapies to avert pain. This review will focus on the rationale for new avenues in pain modulation, including inhibition with anti-NGF antibodies and centrally acting analgesics. The authors also consider the potential for structure modification in cartilage/bone using growth factors and stem cell therapies. The possible mismatch between structural change and pain perception will also be discussed, introducing recent techniques that may assist in improved patient phenotyping of pain subsets in OA. Such developments could help further stratify subgroups and treatments for people with OA in future.

Keywords: analgesia; bone marrow lesions; cartilage; NSAIDs; opiates; osteoarthritis; pain; quantitative sensory testing; subchondral bone; synovium.

Osteoarthritis (OA) is the most common arthritic joint disorder that is typified by significant structural joint damage, functional impairment and pain [1,2]. There are currently no treatments that are known to modify disease progression. At present, licensed treatments for OA are focused on the relief of pain symptoms and other physical treatments aiming to improve function – that is, physiotherapy and rehabilitation [3]. Many people with OA continue to suffer from pain symptoms despite currently available treatments [4,5]. As the incidence of OA continues to rise in an aging population worldwide, there remains a high unmet need to develop new treatments for OA that target symptom relief and improve patients' quality of life [6]. Disability in OA arises from pain, reduced range of movement and diminished control of the affected joint. The pain and functional consequences of OA are responsible for the large burden of morbidity in the community. In a study by Hochberg et al., women (but not men) with OA of the knee had higher morbidity and cumulative mortality rates between the ages of 55–74 years [7]. Increased mortality has also been associated with OA of the knee in Sweden [8]. Although comorbidities may result in the increased mortality, it is important to consider the extent to which OA contributes to the deterioration of an individual's wellbeing. To date, few disease-modifying therapies exist for the treatment of OA. In comparison, inflammatory arthritis, for example, rheumatoid arthritis and psoriatic arthritis, can often be successfully treated with immunomodulatory therapies, including methotrexate and TNF inhibitors, which delay disease progression [9].

This review will highlight areas of recent developments in our understanding of pain in OA. We discuss potential novel therapeutic options for OA pain management, with an evaluation of targets for local mediators in the OA joint, including proinflammatory molecules, neurotransmitters including ion channels, opioids and NGF, together with the modulation of cartilage/bone turnover including agents such as strontium ranelate and bisphosphonates. Local intra-articular therapies for OA could also prove to be effective in future and the authors will discuss the rationale for trials aimed at potential therapies, such as intra-articular FGF-18. Trials are also under way for the use of biological agents including mesenchymal stem cells (MSCs) in the treatment of cartilage defects in OA. While the OA novel treatment pipeline develops, recent work has also focused on optimizing treatment pathways for existing drugs, including NSAIDs, opiates and centrally-acting analgesics, for example, the serotonin–noradrenaline reuptake inhibitor duloxetine in the treatment of OA will also be discussed.

Pathological changes in the osteoarthritic joint

OA is an arthropathy of synovial joints that is characterized by cartilage loss in which there is often evidence of a periarticular bone response [10]. In the early stages of disease, cartilage develops irregularities at the surface where it becomes fibrillated and appears moderately hypercellular [11]. As the condition progresses, deep clefts form in the cartilage, with loss of aggrecan and type II collagen within the cartilage extracellular matrix (Figure 1). Chondrocytes also clump within cartilage, surrounded by regions of intense staining material indicating increased proteoglycan. As ongoing cartilage damage occurs, the articular joint surface is damaged, leading to loss of joint function. Recent work has shown that cartilage is not the only structure undergoing pathological change in OA, and other important structures in the OA joint, for example, bone marrow lesions (BMLs) [12] and synovitis [13] have an impact on pain perception and OA pathophysiology, which will be discussed in further detail in this article.

Clinically, OA can be divided into a number of subsets. Nodal OA is a well-recognized subset, characterized by polyarticular interphalangeal joint involvement of the fingers. There is formation of Heberden's nodes (distal interphalangeal joints) and Bouchard's nodes (proximal interphalangeal joints) [14]. In addition, this subset has a female preponderance, a peak onset in middle age, predisposition to OA of the hip/knee/spine with a marked familial predisposition. OA is a multi-factorial disease in which genetic predisposition, age, estrogen status in women

and environmental agents all contribute to susceptibility. In families with hand OA, a greater concordance exists for monozygotic twins than for dizygotic twins [15]. There is also an increased incidence of hand OA in first-degree relatives [16]. Some studies have investigated the nature of the genetic abnormality in subjects with hand OA.

Associations have been reported with single nucleotide polymorphisms in the human chromosome 2q that are linked with the IL-1 region on this chromosome [17]. Mutations in an extracellular matrix protein, matrilin-3, have also been linked with hand OA [18]. Several studies have found links between OA and HLA status, including the association of HLA-B, -C, -DR and -DQ in two different studies involving European [19] and Japanese [20] cohorts. Pain severity in OA may also have genetic contributions. A functional polymorphism (Val158Met) in the *COMT* gene is associated with painful knee OA [21]. Other gene polymorphisms involving genes implicated in pain perception, for example, *TRPV1*, have been reported to be associated with painful knee OA [22]. With respect to pain sensitivity, TRPV1 and the *PACE4* gene Pcsk6 were associated with pain in knee OA in two separate genetic association studies [23]. Recently, a large consortium genome-wide association studies in 7410 subjects with OA, the arcOGEN study, showed several significant loci relating to cartilage metabolism and obesity [24]. Results showed the most significant association was with the *GLT8D1* gene, associated with glycosylation of cartilage proteins [24]. Other significant associations included the *CHST11* gene, associated with the metabolism of cartilage proteoglycans and the *FTO* gene, which is linked to body weight and obesity. It, therefore, appears that some of the clinically recognized risk factors for OA and mediators of cartilage metabolism are reflected in genetic risk signals, leading to the clinical syndrome of pain and reduced function recognized as OA.

In recent years, there has been a greater understanding of how radiographic changes occurring in the OA joint, including osteophytes, synovitis and BMLs, relate to pain (Figure 2). Typical radiographic features observed by plain radiography, including narrowing of the joint space owing to loss of cartilage, osteophyte formation, bone sclerosis and bone cysts, can be better understood in the context of changes within other joint structures, including synovium and bone, which are aided by MRI techniques [25]. However, it is still unclear as to which changes are most important for pain perception. It has been suggested that BMLs and synovitis have the highest correlations with pain [26,27]. The correlations of pain with synovitis and BMLs will be used as a basis for the discussion of novel therapies for pain in OA in the sections below.

Risk factor modification for OA

Apart from the genetic associations already described, the development of OA is also linked with other risk factors. Several studies have reported a correlation of obesity with an increased risk of knee OA [28–31]. A Finnish group observed 823 subjects without baseline knee OA in which a strong correlation of incident knee OA with BMI was found (odds ratio: 1.75; 95% CI: 1.0–2.8), with a higher odds ratio (odds ratio: 7.0; 95% CI: 3.5–14.1) for the group with a greater BMI (BMI ≥30.0) [29]. The Framingham study also analyzed 598 knee OA subjects who demonstrated an increased risk of incident knee OA with a higher baseline BMI (odds ratio: 1.6 per 5-unit BMI increase; 95% CI: 1.2–2.2) [28]. The Chingford study found obesity to be a predictor for the development of contralateral OA in women with unilateral OA [32]. Such results supporting the risk of heavier individuals developing OA are important to consider when discussing modifiable risk factors for OA [33]. Weight loss and exercise are popular interventions for OA [34]; how they influence OA progression and pain is further discussed in the following section.

Exercise & weight loss

In the case of exercise therapy for OA, land-based or water-based exercise and strength training have been subjected to meta-analyses. Four meta-analyses have found there to be small, but clinically relevant short-term benefits of land-based exercise for pain and physical function in knee OA [34–37]. The duration and type of exercise programs included in the meta-analyses varied quite widely, but interventions often comprised a combination of elements, which included strength training, active range of motion exercise and aerobic activities. Although results were favorable in most types of land-based exer-

Key points

- **Genetic Factors:** COMT and TRPV1 polymorphisms link to knee OA pain severity.
- **BMI Risk:** Higher BMI increases knee OA risk; odds ratios up to 7.0 for BMI ≥30.
- **Imaging Insights:** BMLs and synovitis strongly correlate with OA pain.
- **Holistic Management:** Address genetic, biomechanical, and lifestyle factors for effective OA treatment.

Key points

- **Exercise Efficacy:** T'ai chi and strength training significantly improve pain and function in knee OA.
- **Weight Loss Benefits:** A 5% reduction in weight over 20 weeks significantly alleviates knee OA pain and disability.
- **Osteophyte Dynamics:** Osteophytes stabilize joints but can also induce nociceptive pain through nerve compression.
- **Surgical Impact:** Removing osteophytes during joint replacement enhances pain relief and functional recovery.

cise, no specific exercise program appeared to be more favorable [34–37]. Of note, meta-analyses investigating t'ai chi found favorable benefits in improving pain and physical function in people with knee OA [38,39]. With respect to strength training, a meta-analysis and systematic review published in 2011 showed moderate effect sizes for reducing pain and improving physical function compared with controls [34]. Of note, recent data from MOST suggested that people with knee OA had significant levels of knee instability, which was associated with fear of falling, poor balance confidence, activity limitations and reduced physical function [40], which can all have an impact on the level of physical activity achievable by people with OA by exercise interventions [40]. Although there are reports, particularly from animal models, of high physical activity worsening OA lesions [41], clinical studies have been less clear and current guidance recommends exercise for amelioration of pain and improved function in OA.

Recent reports have outlined the rationale for weight reduction in OA in recommendations from both EULAR [42] and OARSI [43]. In 2007, Christensen et al. published a meta-analysis and systematic review of weight management in OA [44]. The authors found reductions in pain and physical disability for overweight participants with knee OA after a moderate weight reduction regimen [44]. The authors reported that a weight loss of 5% should be achieved within a 20-week period, that is – 0.25% per week, for the treatment to have efficacy for pain relief and improved function.

Osteophytes & their effect on OA pain

Osteophytes, sometimes described as osteochondrophytes or chondro-osteophytes, are a classical feature of OA joint pathology (Figure 2), and are found in people with OA and in experimentally induced models. They can appear early in OA, often a precursor to joint space narrowing. Resulting from endochondral ossification at the margins and areas of cartilage loss in OA joints, these structures arise within tissue close to the chondrosynovial junction from progenitor cells. Progenitors may include MSCs residing within the perichondrium and synovium [45,46], suggesting there is a reserve of pluripotent cells receptive to joint injury. By examining osteophytes of distinct developmental stages within patients, a successive pattern of differentiation can be seen [47]. At first progenitor cells at the osteochondral junction are stimulated by growth factors, such as TGF-**β** and basic FGF, to proliferate [48]. The cells within the chondrophyte undergo chondrogenesis and deposit extracellular matrix proteins, such as aggrecan and glycosaminoglycan. Within the early osteophyte, chondrocytes undergo hypertrophy followed by endochondal ossification, deposition of bone and formation of marrow cavities. Once the mature osteophyte is fully formed, it will integrate with the subchondral bone and the original cartilage [46,49]. Osteophytes are considered to be an adaptive reaction of the joint to mechanical stress and instability. It has been suggested that they may provide a compensatory role to redistribute weight bearing forces and stabilize joints affected by malalignment and OA [48,50,51]. Osteophytes are often removed at the time of joint replacement surgery or cheilectomy procedures, removing the mechanical pressure they apply to surrounding structures. More recent techniques of unicompartmental joint replacement surgery targets areas that may be specifically affected by such lesions and, therefore, have a good impact on pain and joint translocation in the long term [52]. Osteophytes cause joint pain by stretching and compressing nerves and compromising blood flow, possibly causing motor, sensory impairment and faintness, and, in worse cases, impact surrounding tissue and organs [45], while some osteophytes are asymptomatic and could form within healthy individuals. Reports demonstrate that antiresorptive drugs that prevent the formation of cancellous subchondral bone have no effect on the development of osteophytes. Similarly, no inhibition is seen with doxycycline; however, anti-inflammatory drugs, such as glucocorticoids, have an anti-anabolic effect and halt osteophytosis [53–55]. It is evident that the role osteophyte have on pain and function is dependent on their location and disease stage, in end stage OA of larger joints they may act to stabilize the degenerated joint, while osteophytes of the spine are often painful and debilitating [48].

BMLs & OA pain

Several studies have demonstrated the correlation of BMLs with pain, particularly in

large joint arthritis [27,56]. This field has advanced owing to the development of MRI techniques, which have optimized the use of such technologies in visualizing lesions at the bone–cartilage interface. BMLs are often described as diffuse areas of high-density signal in a T2-weighted, fat-saturated MRI or in short tau inversion recovery sequences (Figure 2) [57]. BML patterns on MRI have been described using various methods, some measured using a binary [58] or semiquantitative method (whole-organ MRI score or 0-3 scale) [59,60] for the presence of lesions, several looking at distribution (global and focal cystic) [61], others based classification on lesion location to the lateral and medial condyle [62], while some addressed changes in BML size based on quantitative measurements (maximal diameter or area of lesion) [63,64]. Although changes in BMLs have been analyzed by a number of methods and measurements, this has not significantly affected the general findings [65]. In a study of people with severe hip OA undergoing total hip replacement, Taljanovic et al. found that the quantity of BMLs measured by MRI correlated with severity of pain and the number of microfractures observed by histology [66]. This study was relatively small since data were acquired on 19 patients; however, there are now larger clinical data sets observing the relation of BMLs to pain in OA [12,67,68]. The MOST study, which evaluated 570 subjects, found that the severity of BMLs and synovitis were associated with fluctuation of frequent knee pain and pain severity [12]. MOST also showed that of the two types of structural lesions, BMLs were a better predictor of knee pain. In contrast, other groups have not been able to confirm the correlation of pain with BML as strongly as the MOST investigators [68], although larger BMLs have a more significant correlation with pain [69].

With respect to changes in BML over time, Garnero et al. evaluated 377 patients with painful knee OA, reporting that within 3 months, BML scores decreased in 37 and increased in 71 patients [70]. Assessing 182 patients with OA at baseline and at 2-year follow-up, Kornaat et al. reported that total size of BML changed in 66% of patients, with change in size of individual lesions as 45%, new lesions appeared in 21%, and existing lesions completely disappeared in 10% of patients [71]. The authors concluded from their study that in OA, BMLs are part of a dynamic process and not a constant finding, as opposed to cartilage loss. BMLs are often associated with other MRI features in OA, including subchondral cysts [72], which are a well-defined area of fluid signal on MRI. Several longitudinal investigations have shown that areas of BML are related to subchondral cysts and that BMLs could be an early precystic lesion. Carrino et al. suggested that cysts arise from the regions of BML, and signal size of BML changes with cyst development [72]. While others reported that when BMLs and cystic lesions are in close proximity, the direction in which they change is identical [71]; however, not all BMLs will give rise to a cyst. Histologically, a number of pathologies are seen in BMLs, ranging from edema, fibrosis, osteonecrosis, trabecular abnormalities to bony remodeling [73]. At present, the cause(s) for BML development are not certain, but several possibilities have been suggested. Hunter et al. proposed that changes in BMLs are in part mediated by limb alignment since medial BMLs occurred mostly in subjects with varus-aligned limbs, and lateral lesions occurred in those with valgus-aligned limbs [74]. It has been suggested that BMLs develop as a result of subchondral bone ischaemia [75], which impairs the exchange of nutrients and oxygen with articular cartilage. Such pathological processes could reduce cartilage integrity and increase the risk of OA development [76–78]. Some hypothesize that BMLs are a result of bony microcontusions leading to necrosis, or increased intra-articular pressure resulting in the extension of synovial fluid into the subchondral bone and proliferation of myxomatous tissue within bone marrow. A similar theory suggest that BMLs may develop if synovial fluid is pumped into subchondral bone marrow through defects in articular cartilage, or from increased stress placed on the subchondral bone owing to overlaying articular cartilage loss – potentially resulting in subchondral microfracture and marrow edema [79]. Felson and colleagues demonstrated BMLs are more likely to be present in painful knees as opposed to nonpainful knees, finding large BMLs in 37% of patients with symptomatic radiographic OA compared with 2% in the asymptomatic patients ($p < 0.001$) [56], which was confirmed by Sowers et al. [68], but not by Kornaat and colleagues [80]. BMLs were also strongly associated to cartilage loss, primarily within areas overlying the lesion [74]. At end stage OA, the joint

Key points

- **Pain Management:** Monitor and assess BMLs through MRI as they correlate strongly with pain severity, informing pain management strategies in knee OA.
- **Intervention Timing:** Recognize that changes in BMLs indicate a dynamic process; timely interventions may prevent further joint degeneration.
- **Targeted Therapy:** Consider therapies aimed at reducing BML size and associated pain, particularly in patients with larger lesions, to improve functional outcomes.
- **Assessment of Alignment:** Evaluate limb alignment, as BML development may relate to varus or valgus alignment, potentially guiding corrective interventions in OA management.

Key points

- **Bone Marrow Lesions (BMLs):** MRI-detected BMLs correlate with pain severity in OA patients, particularly in large joints, indicating their potential as pain biomarkers.
- **Dynamic Nature:** BMLs change over time, with studies showing that sizes of lesions can increase or decrease, suggesting they are part of a dynamic pathological process.
- **Association with Other Lesions:** BMLs are often associated with subchondral cysts and cartilage loss, complicating the identification of pain sources in advanced OA.
- **Treatment Interventions:** Bisphosphonates have shown limited efficacy in pain relief for OA, with some studies suggesting potential benefits, particularly with zoledronate in knee OA.
- **Strontium Ranelate:** This drug has demonstrated efficacy in reducing joint space narrowing and pain in moderate OA, supporting its consideration in treatment regimens.

harbors many pathological features that contribute to arthritic pain. Owing to this coexistence of such defects, it is difficult to determine which single lesion activates and causes pain. Investigators are currently examining how specific MRI changes correlate with clinical features of OA pain in longitudinal studies as this will be helpful in considering avenues for novel therapies [81].

With respect to therapeutic interventions aimed at modulation of BML, recent work has focused on potential use of drug interventions that have previously been utilized to modulate bone density, for example, bisphosphonate drugs. Bisphosphonates are a class of drugs that inhibit osteoclast bone resorption. A recent meta-analysis by our group evaluating studies involving 3832 patients with OA of the hand, hip, knee and spine found that, overall, bisphosphonates showed limited efficacy in analgesia for OA [82]. However, a few studies did show benefit with specific drugs in the class. In the two largest studies that tested the effects of risedronate in knee OA [83,84], our meta-analysis showed no statistically significant difference in pain or functional outcomes assessed by Western Ontario and McMaster Universities OA Index (WOMAC) with risedronate over placebo arms at doses of 5 mg daily, or 15, 35 and 50 mg weekly. The remaining studies, which could not be evaluated by meta-analysis, showed that bisphosphonates reduce pain greater than placebo or nonreatment controls in OA in Asian, European and North American populations when assessed by visual analog scale and WOMAC outcomes. There was heterogeneity across the studies analyzed, with variability in anatomical position of disease, gender studied, route and frequency of drug administration. Specifically, zoledronate has been used in intravenous formulation in a trial of patients with knee OA. Laslett et al. compared clinical outcomes between a single infusion of zoledronate (5 mg/100 ml) to a placebo control group [85]. This trial showed significant improvements in pain using the visual analog scale at 6 months, which was the primary end point of this study. The authors also reported a reduction in total BML area of greater magnitude in the zoledronate group compared with placebo after 6 months (–175.7 mm2; 95% CI: –327.2 to –24.3) with a nonstatistically significant trend after 12 months (–146.5 mm2; 95% CI: –307.5–14.5). With respect to adverse events, the most common was cold or flu symptoms, which was 78% of the 90% total [85]. In other reports, a flare-up of OA pain and inflammation has also been described with zoledronic acid infusion [86]. It is, therefore, possible that drugs targeting bone turnover may be increasingly considered for modulating processes targeting bone turnover in OA; however, further work is required in this area. In more recent work from Nishii et al., 50 participants with symptomatic hip OA were randomized to treatment with alendronate (35 mg/week and 600 mg/day calcium lactate) or a control group (600 mg/day calcium lactate) for 2 years [87]. Alendronate treatment by standard dose for osteoporosis showed clinical efficacy for decreasing pain, but failed to show preventative effects for structural progression of hip OA. Recent data reported from the NIH OA Initiative cohort of subjects with knee OA investigated changes in pain scores in participants taking bisphosphonate therapy [85]. The study reported significant reduction in numeric rating pain within the first 3 years of bisphosphonate use, with reduction in effects by year 4, possibly owing to reduced compliance. A sample size of 55 patients who were bisphosphonate users was studied and, therefore, larger studies would be useful for further evaluation of therapeutic effects.

Recently, a clinical trial has also been published on the use of another bone modulator: strontium ranelate in the treatment of OA [88]. Strontium ranelate is already licensed for use in osteoporosis. Strontium ranelate is a strontium (II) salt of ranelic acid and is known to increase deposition of new bone by osteoblasts and reduce bone resorption by osteoclasts. A recent double-blind, randomized, placebo-controlled trial, investigated its potential efficacy in OA pain. Reginster et al. reported outcomes for patients who had moderate OA of the knee, with Kellgren and Lawrence grade 2/3 and joint space width of 2.5-5 mm [88]. Patients were randomized to either strontium ranelate 1 g/day (n = 558), 2 g/day (n = 566) or placebo (n = 559). This study reported that the rate of disease progression measured by joint space narrowing was reduced in the strontium ranelate group at 1 or 2 g daily compared with placebo. The study group also reported greater reduction in WOMAC pain subscore (p = 0.028) and knee pain (p = 0.065) with strontium ranelate 2 g/day after 3 years of treatment. A more recent analysis of the use of strontium ranelate in

the same study showed disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee OA study SEKOIA using quantitative MRI [89]. The authors showed a reduction in BMLs protects against cartilage loss.

In the future, it remains to be seen whether the tolerability of an agent, such as strontium ranelate, would be sustained for more than 5 years, and if taking such a drug for a certain period of term confers chondroprotection and pain relief or whether indefinite use is required. It should also be recognized that patients at risk of developing deep vein thrombosis and myocardial infarction cannot be prescribed strontium ranelate, suggesting that such an agent would require careful screening and monitoring in the OA population.

Further studies have recently been published reporting the use of specific pharmacological agents to target OA pain. These include a study by Esenyel et al. in which nasal calcitonin was assessed for the treatment of knee OA [90]. This study of 220 postmenopausal women demonstrated a significant improvement in pain ($p < 0.001$), stiffness ($p < 0.05$) and functional level ($p < 0.05$) after 1 year of treatment. Other emerging studies, albeit in animal models so far, suggested that inhibition of specific proteases, for example, cathepsin K, could be beneficial in OA treatment. For example, Hayami and colleagues reported that a cathepsin K inhibitor was able to reduce cartilage degradation and osteophyte formation in a rabbit model of OA [91]. Cathepsin K inhibition has also been shown to reduce type II collagen degradation in a guinea pig model of OA[92]. Other agents such as parathyroid hormone have also been shown to improve the structure of articular cartilage, but the effect of parathyroid hormone on pain in OA is as yet unknown [93].

Targeting synovitis to treat OA pain

Synovitis is a process characterised by inflammation. It is increasingly recognized that synovitis is a key factor associated with the signs and symptoms of OA, including joint swelling, stiffness and pain [94], which all indicate the presence of synovitis due to a thickened synovium or effusion. Synovitis, which involves the penetration of mononuclear cells into the synovial membrane and the production of prinflammatory cytokines, such as IL-1, IL-6, TNF-**α** and granulocyte macrophage colony-stimulating factor are upregulated in OA tissue (Figure 3) [95]. There is also increased expression of VEGF and matrix metalloproteinase (MMP) expression in OA synovial tissue, but at significantly lower levels than in patients [94].

Gadolinium-enhanced MRI and ultrasonography are useful and convincing tools for the observation of synovitis [96]. Studies using such methods of imaging suggest that the presence of synovitis may be a marker for the severity and increased risk of the radiographic progression of OA. Systemic high-sensitivity C-reactive protein levels have been reported to mirror synovial inflammation in OA patients and correlate with increased pain [97]. How and why the synovium becomes inflamed during the development of OA has been investigated. One hypothesis is that degraded cartilage fragments, such as advanced glycation end products, contact the synovium: these fragments are recognized as foreign bodies and prompt the synovial cells to produce inflammatory mediators from within the synovium and adjacent cartilage (Figure 3). These mediators are suggested to activate chondrocytes present in the superficial of the cartilage, leading to MMP synthesis and perpetuating cartilage degradation. Such inflammatory mediators may also be involved with synovial angiogenesis and could increase the synthesis of inflammatory cytokines and MMPs by the synovial cells themselves, initiating an irreversible positive feedback cycle [98]. Another theory proposes synovial tissue to be a primary trigger in OA, along with many other cell types involved in many immunological processes have been linked to the initiation and progression of OA [99]. Recently the importance of synovial gene expression to global joint pathology has been supported by the abundance of the synovial fluid proteome with distinct profiles found in healthy individuals compared with early OA in people undergoing arthroscopy after injury of the medial meniscus and late-stage patients undergoing joint replacement [100]. Other findings have also suggested a central role for complement in low-grade inflammation in OA. Proteomic and transcriptomic analyses of synovial fluid and synovial tissue from individuals with OA showed expression and activation of complement in human OA joints [101]. Authors showed that mice genet-

Key points

- **MRI Changes:** Research links specific MRI changes to clinical OA pain, guiding future therapies.
- **Bisphosphonates:** Limited analgesic effect in OA; zoledronate shows potential pain relief.
- **Strontium Ranelate:** May reduce knee OA pain and progression; long-term use requires more study.
- **Synovitis Monitoring:** Imaging synovitis helps assess OA severity and informs treatment.

Key points

- **Corticosteroids:** Intra-articular corticosteroids show initial benefits for OA, but effects diminish over time; low-dose oral corticosteroids lack efficacy for hand OA.
- **Disease-Modifying Drugs:** Methotrexate and hydroxychloroquine may target OA mechanisms beyond synovial inflammation and could be considered for treatment.
- **Doxycycline:** While doxycycline can slow joint space narrowing in knee OA, it has minimal pain relief and poor tolerability due to side effects.
- **NSAIDs & COX-2 Inhibitors:** NSAIDs are first-line treatments for OA, but careful monitoring for cardiovascular and gastrointestinal risks is essential, particularly in older patients with comorbidities.

ically deficient in complement component 5 (C5), C6 or the complement regulatory protein CD59a did not develop OA in comparison to their wild-type counterparts in three distinct animal models of OA. The expression of the matrix degrading enzyme MMP-13 colocalized with the complement complex in chondrocytes around osteoarthritic cartilage. It is, therefore, conceivable that molecules targeted to such areas may be of use in the inhibition of cartilage injury in the initial steps during the development of OA.

Synovitis has been targeted with both intra-articular and systemic corticosteroid treatment in previous trials with good effect (Figure 3) [102]. However, the effects of such agents do not appear to be sustained over time. This has led to several researchers calling for the potential need for use of conventional disease-modifying drugs in OA, including methotrexate [103] and hydroxychloroquine [104]. It is interesting to note that corticosteroids in the form of low-dose prednisolone were not shown to be effective in a clinical trial of hand OA [105]. It could therefore be argued that in OA, where low-dose oral corticosteroids are not efficacious, the potential mechanism of disease-modifying anti-rheumatic drugs such as methotrexate and hydroxychloroquine, may be targeted at other compartments apart from synovium, for example, cartilage or bone.

Other groups have argued that more targeted therapies, for example, towards MMP, may be considered. In the largest study of its kind using doxycycline, which inhibits MMP activity, placebo was compared with doxycycline in women with unilateral knee OA [106]. The trial involved treatment with doxycycline 100 mg twice daily in the treatment arm versus placebo, also given twice daily. A total of 431 patients were recruited and showed that after 30 months treatment, doxycycline slowed the rate of joint space narrowing in affected knees. Of interest, drug intake had no effect on joint space narrowing in the contralateral knee, suggesting other factors may also be at play. A recent meta-analysis that included a more recent study showed that doxycycline conferred no overall benefit in pain, with a minimal improvement in joint space narrowing that was outweighed by poor tolerability of the drug owing to side effects [107].

NSAIDs & nutraceuticals treatment

Traditionally, proinflammatory mediators have been targets for the inhibition of inflammation and consequently pain (Figure 3). NSAIDs inhibit the COX pathway, thereby inhibiting action of prostaglandins and leukotrienes in the OA joint. They are recommended as the first line of treatment for moderate-to-severe OA, used by 20–30% sufferers [108,109], despite the number of individuals who die from NSAID toxicity every year [110,111]. NSAIDs have been one of the most frequently used drugs for over 30 years with 80% of rheumatologists prescribing NSAIDs for symptomatic OA [112–114]. More recently, the second-generation COX-2 inhibitors (rofecoxib, etoricoxib and lumiracoxib) were favored as a safer alternative with superior specificity and efficacy reducing the number of adverse events. However, it was not long before these were also associated with a higher risk of cardiovascular- and gastrointestinal-related adverse events [115,116]. Ultimately, in 2007, the US FDA issued a medication guide for NSAIDs recommending physicians to prescribe the lowest dose for the shortest time possible [117].

Some of the landmark studies of COX-2 inhibitors were conducted in patients with large joint OA; which is especially painful and debilitating [118]. Compared head-to-head, celecoxib and etoricoxib are equally effective in improving pain responses in subjects with hip or knee OA [119]. One of the major issues regarding prescription of NSAIDs is that the population group with OA are often older and may have other significant comorbidity including cardiovascular disease. A meta-analysis of the MEDAL study found that etoricoxib was associated with a higher incidence of hypertension in comparison with diclofenac in people with arthritis [119]. The same meta-analysis suggested that treatment of hypertension with calcium-channel blockers and concurrent NSAID use afforded better control of blood pressure in comparison with other antihypertensive agents assessed.

While NSAIDs provide a short-term relief for OA pain, it is important to consider the long-term effects of anti-inflammatory treatment for a condition primarily initiated by articular cartilage degeneration that can be associated with synovitis. It has been questioned

whether there a correlation between the sudden increase in OA: with replacement surgeries between 1997 and 2005 significantly rising: knee replacement's climbing by 69%, hip replacements by 32% and spinal fusion surgeries increasing by 73% [120], and the widespread use of NSAIDs over the last 30 years. It is also possible that extensive use of NSAIDs and the increase in OA is probably mainly owing to the growing number of elderly and obese individuals. The LINK study tested the effect of indomethacin and tiaprofenic to placebo on radiographic progression of OA in 812 patients [121]. After 1 year of treatment on 376 patients the indomethacin group showed 47% progression of radiographic modifications of OA, while placebo demonstrated only 22%. When comparing this to the tiaprofenic acid group where radiographic progression of OA was similar in both the treatment and placebo group (43 and 34%, respectively), it was concluded that indomethacin accelerated structural damage in OA and this branch of the study was terminated [121]. The majority of reports of NSAID efficacy and tolerability suggests that they do have efficacy for OA pain, particularly in the knee [122,123], but that dosing should be titrated to relative comorbidity and tolerability, with use being focused at times of flare or high symptom severity. At present, guidelines favor the use of topical versus oral NSAIDs if they are efficacious, or oral NSAIDs in severe symptomatic disease for as short a duration as possible [124].

In the quest for novel therapeutic targets for OA pain, several studies in recent years have aimed to compare newer agents to existing therapies for pain. The GAIT trial compared the nutraceuticals glucosamine 1500 mg daily, chondroitin sulphate 1200 mg daily, celecoxib 200 mg daily or placebo in a large randomized trial over 24 weeks [125]. The most rapid response to pain relief was achieved by the celecoxib group, in which the highest number of patients achieved a 20% reduction in the summed score for the pain subscale of the WOMAC index [125]. Although the glucosamine and chondroitin sulfate groups did not achieve superior analgesic relief compared with the celecoxib group in this study of people with knee OA, more recent work has suggested that the nutraceuticals may be of benefit for analgesic relief in a subgroup of patients [126]. Reginster et al. also showed improvement in joint space narrowing in people with knee OA treated with glucosamine [127,128]. However, with respect to disease modification, a systematic review has found no statistically significant differences in minimum joint space narrowing between glucosamine and placebo at 1-year follow-up, although a moderate effect was detected at 3 years [129]. Similarly, in the case of chondroitin, four systematic reviews have examined the efficacy of chondroitin for knee OA [129–132]. Results have varied regarding symptom relief, with some reviews finding no significant benefit of chondroitin over placebo and others finding large effect sizes in favor of chondroitin. Results have also been mixed regarding disease modification, with only some studies showing statistically significant decreases in joint space narrowing over a longer 2-year follow-up [129,132].

Other agents targeting glycosaminoglycans turnover in the joint include hyaluronic acid derivatives [133–135]. Hyaluronan is a normal constituent of the synovial joint synthesized by chondrocytes in cartilage and also present in the synovial fluid. It serves to create high viscosity in synovial fluid and buffers fluid loss from joints. A number of formulations have been subjected to clinical trials, including hylan and hyaluronic acid derivatives [133–135]. Most of the trials have been conducted in subjects with painful knee OA. The usual protocol for most of these studies has been repeated injections of hyaluronic acid, for example, series of three injections at weekly intervals. The primary outcome measures included assessment of pain by WOMAC scores. Juni et al. showed improvement in pain scores in subjects receiving three different forms of hyaluronan [133]. Of note there, were more adverse effects in the hyaluronan derived from avian sources in comparison with bacterial sources. In this non-industry conducted study, a therapeutic response to pain was maintained even at 6 months. More recent studies have included control arms, for example, hyaluronic acid was superior to saline injection [134] but less effective to corticosteroid injection in the knee [135]. Although a number of studies have described efficacy of hyaluronic acid for pain, especially in knee OA, as outlined above, a recent meta-analysis by Bannuru et al. reported no superiority of hyaluronic acid over treatment with NSAIDs [136]. The authors of the meta-analysis did suggest that hyaluronic acid formulations may have some advantages over NSAIDs with respect to safety [136].

Key points

- **NSAID Impact:** The increasing prevalence of OA and related surgeries may be linked to the extensive use of NSAIDs; however, indomethacin has been shown to accelerate structural damage in OA.
- **Efficacy of Topical NSAIDs:** Current guidelines recommend using topical NSAIDs or limiting oral NSAID use to acute flare-ups due to associated comorbidities and potential adverse effects.
- **Nutraceuticals for Pain Relief:** The GAIT trial indicated celecoxib provides the quickest pain relief compared to glucosamine and chondroitin; however, nutraceuticals may benefit specific patient subgroups.
- **Hyaluronic Acid:** Hyaluronic acid injections show some efficacy in pain relief for knee OA, but recent meta-analyses suggest no significant advantage over NSAIDs, highlighting the need for careful treatment selection.

Key points

- **NGF Targeting:** Monoclonal antibodies to NGF can significantly reduce OA pain but may cause rapid OA progression in some patients.
- **Current Trials:** Anti-NGF therapies are being tested with and without NSAIDs or opioids.
- **Growth Factors:** Anabolic factors like FGF-18 are being studied for their potential to repair cartilage in OA.
- **Platelet Therapies:** Platelet-rich plasma may enhance cartilage health and reduce inflammation in OA.

NGF monoclonal antibodies

Since there is a significant side-effect profile associated with long-term use of NSAIDs and opiate analgesics, recent interest in novel pain targets has grown. There has been a focus on NGF as a therapeutic target for pain. In contrast to TNF, NGF acts primarily through a direct action on sensory neurons to induce hyperalgesia. NGF injection into animals leads to prolonged hyperalgesia and allodynia [137]. Increased NGF production has been observed in rheumatoid arthritis and OA synovial cells and chondrocytes [138]. The first clinical trial of a humanized monoclonocal antibody to NGF that binds to and inhibits NGF was published in 2010. In this study, Lane and colleagues reported that 450 patients with knee OA who were randomly assigned to treatment with anti-NGF antibody at 10, 25, 50, 100 and 200 μg/kg bodyweight achieved impressive reductions in walking pain scores measured using the WOMAC index, with a mean of 45–62% reduction with varying doses of tanezumab compared with a placebo response of 22% ($p < 0.001$) [139]. However, a major concern over this trial was the observation of rapidly progressive OA in a subgroup of such patients and hence the halting of some ongoing trials due to this concern at that time [140]. It has been suggested that the very successful inhibition of the NGF target in some patients could have led to rapidly progressive OA in such cases, and further analysis of this data set is being carried out [141]. Trials of anti-NGF have now resumed and are in progress, for example, tanezumab and fulranumab. More recent studies have also been published to assess the effect of tanezumab in combination with NSAIDs [142] and opioid analgesics [143]. It will, therefore, be interesting to note whether, in a subgroup of patients, particularly those who are not taking NSAID drugs, that anti-NGF inhibition may be a validated therapeutic target in OA.

Growth factors & stem cell therapy

During development biosynthesis is stimulated by a variety of anabolic cytokines and growth factors, such as TGF-**β**, bone morphogenetic proteins and FGF. In OA, many factors, such as inflammatory cytokines TNF-**α** and IL-1, are produced by the synovium and the chondrocytes. In normal adult cartilage, chondrocytes synthesize matrix components very slowly and there is strict regulation of matrix turnover: a delicate balance between synthesis and degradation. In OA, however, this balance is disturbed, with both degradation and synthesis usually enhanced until changes in both bone cells and chondrocytes favor catabolic activity: proinflammatory cytokines, including IL-1, TNF-**α** and IL-6, act to increase the synthesis of MMPs, decrease MMP enzyme inhibitors and decrease extracellular matrix synthesis. The initiation of such degradative alterations in the joint leads to the depletion of cell reservoirs, loss of the condrogenic potential of cartilage bringing about the preponderance of a fibrogenic phenotype and the structural and functional failure of the joint [144]. Current treatments for cartilage defects in early OA include surgical interventions (microfracture and osteochondral auto/allo-grafts), which have shown promise in clinical trials [145].

Such catabolic changes may have the potential to be reversed by the use of a pool of growth factors [146]. The FGF family of growth factors regulates branching morphogenesis and limb development [147]. FGF-18 is thought to have an anabolic effect on cartilage, leading to increased deposition of FGF-18 in the ribs, trachea, spine and joints. Preclinical data of the anabolic effects of FGF-18 is now being followed-up by Merck Serono in Phase I clinical trials [147]. Investigators are currently looking into the therapeutic potential of endogenous plasma rich in growth factors that may have the potential to modulate gene expression of chondrocytes, synoviocytes, macrophages and MSCs. Therapies involving the utilization of growth factors could have the possibility to stimulate an anabolic microenvironment within an affected joint. A possible approach to maintaining the homeostasis of damaged OA joint tissue could be the use of growth factors, which in turn could improve cartilage/bone dysregulation and lead to reduced pain and improved function [146,148]. Platelet-derived elements, such as platelet-rich plasma, human platelet lysate and platelet supernatants, are carriers of endogenous morphogens, which can be stimulated by endogenous or exogenous activators to modulate cell fate, encouraging cell proliferation and matrix synthesis, alongside anti-inflammatory effects owing to the downregulation of catabolic pathways [148,149]. Platelet-derived elements are conve-

nient and easy to extract, with a high-speed recovery potential offering multiple growth factors at an affordable cost [149]. Platelet-rich plasma injections have had beneficial effects in the treatment of mild-to-moderate OA in approximately 6 months compared with hyaluronic acid and neutral saline injections [148]. Experimental, preclinical and clinical studies are being reported suggesting short-term (1–2 years) improvement, but long-term results on cartilage injuries and joint pain are unknown [149].

MSCs are multipotent precursors of connective tissue cells that can be isolated from a wide variety of adult human tissues, including synovial joints. Endogenous MSCs could possibly act as reservoirs for cell repair or immunomodulatory sentinels reducing inflammation [144]. Current methods rely on the paracrine properties of MSCs that release several growth factors, such as HGF, IGF and TGF, along with anti-inflammatory factors, including cytokines, IL-1ra, indoleamine 2, 3-dioxygenase and HLA antigen-G5 [150]. Chondrocyte and osteoblast phenotypes are established via the activation of pathways induced by paracrine factors, such as the SMAD cascade by BMP-2, TGF-3 or Wnt signaling [151]. Thus, the paracrine factors delivered by the MSCs may be more important for MSC therapeutic potency than stimulating repair responses for the differentiation of cells [144].

Early exploratory research studies used MSC-derived chondrocytes to regenerate cartilage in OA. A hydrated collagen matrix covered with MSCs was implanted into the joint; cartilage regeneration was complete after 6 months, although 20–100% of the new tissue had not integrated into the original cartilage [151,152]. Intervention with local delivery of ex vivo cultures of MSCs, as the chondrogenic potential of adult chondrocytes are lost and regression into a fibrotic phenotype initiates, in preclinical models of joint disease has led to promising outcomes and is now being tested in clinical trials recently started in 2013 [144]. Several early-stage clinical trials testing the delivery of MSCs via intra-articular injection into the knee are underway; however, the optimal dose and vehicle are still being optimized [144]. Bader and Macchiarini recently demonstrated the uses of stem cell techniques in several pioneering transplant surgeries, seeding an inert tracheal scaffold with either patient or donor bone marrow MSCs [153]. Further work is needed to characterize factors that could avert MSC derived chondrocyte to undergo premature hypertophy and understand what facilitates terminal development pathways for stable hyaline cartilage regeneration [154]. In the case of both anabolic agents, such as FGF-18, and stem cell therapy trials currently underway, it will be interesting to observe if therapies targeted at regeneration of damaged cartilage in people with OA will translate into improved outcomes for pain and function in the medium to long term.

Pain sensitization in OA

In chronic arthritis, a complex set of activation signals lead to the persistence of nociceptive pain. These include known molecular mediators of pain, such as substance P, prostaglandin E2, NGF, TNFR-**α**, bradykinin, GDNF and TRPV1 (Figure 3). Recent work has focused on tools to measure pain peripherally and centrally in people with OA (Figure 4). Several groups, including work in our unit, have reported the use of quantitative sensory testing in people with OA [155–158]. Pain threshold testing using algometers has become more widely accepted for measuring pain perception objectively since it is reproducible over time and has been validated in large studies with knee OA [159] or intra-oral pain [160]. We have found quantitative sensory testing to be a useful objective measure of hand OA pain [158] where people with hand OA showed evidence of peripheral sensitisation. A recent meta-analysis of pain pressure threshold testing in OA showed that pain pressure thresholds demonstrated good ability to differentiate between people with OA and healthy controls [156]. Lower pain pressure thresholds in people with OA in affected sites may suggest peripheral, and in remote sites central, sensitization. Recent studies have also shown that certain patients with OA may remain sensitized to pain even after joint replacement surgery [161].

Brain neuroimaging tools have also been used to investigate sensitization in OA. Gwilym et al. reported increased activation of brain pain processing centers with functional MRI in chronic hip OA, including the thalamus, anterior cingulate and insular cortex, upon quantitative sensory testing [162]. Kulkarni et al. reported similar activation using fludeoxyglucose PET in knee OA, sug-

Key points

- **Consider Platelet-Rich Plasma:** Effective for mild-to-moderate OA; offers potential benefits in pain management.
- **Explore MSC Therapy:** Promising for cartilage repair and reducing inflammation, but optimal dosing and delivery methods are still under investigation.
- **Acknowledge Pain Sensitization:** Chronic OA pain may be exacerbated by peripheral and central sensitization, necessitating tailored pain management strategies.
- **Utilize Quantitative Sensory Testing:** An objective tool to assess pain thresholds in OA, aiding in the evaluation of treatment efficacy and patient progress.

Key points

- **Central Sensitization:** Chronic OA pain activates brain areas like the thalamus and cingulate cortex, indicating hypersensitivity.
- **Duloxetine Use:** Duloxetine offers better pain relief than placebo and is safe for patients who can't tolerate NSAIDs or opioids.
- **Pain-Structure Link:** Pain in OA does not always correlate with structural damage, highlighting the complexity of pain mechanisms.
- **Early Intervention:** Combining drugs with pain management early may prevent chronic pain, needing further clinical validation.

gesting activation of distinct brain regions in patients with chronic arthritic pain [163]. Several authors have described the phenomenon of chronic pain center activation during arthritis as central sensitization, a process thought to derive from hypersensitivity to stimuli by long-term activation of peripheral receptors in arthritic joints. A study by our group in people with hand OA showed significant activation in the thalamus, cingulate and insular cortex but not controls [164]. Of interest, the cingulate cortex is involved in developing emotion formation, learning and memory, suggesting that people with OA are adapting their responses to sensory cues in their hand and developing unique pain activation systems compared with controls. Others have suggested that the cingulate cortex is important in mediating affective processing of pain [165]. With increasing information regarding sensitization in OA, recent trials have reported the use of centrally acting agents, such as the selective serotonin and noradrenaline reuptake inhibitor duloxetine in the treatment of OA [166]. In a recent review, Brown and Boulay discuss the evidence for the efficacy of duloxetine use in four chronic pain conditions including OA [167]. They report that the studies published so far demonstrate a superior analgesic effect of duloxetine compared with placebo that is sustained with continued use and is also safe and effective when used concomitantly with NSAIDs. Further information on the cost utility of duloxetine has shown that it would be cost effective when evaluated in a US population and could be particularly useful in the over 65-year age group when NSAIDs have been prohibitive owing to side effects [168]. Other work by Micca et al. has shown that duloxetine is safe in younger and older people with knee OA [169]. Analgesics, such as duloxetine, may have an important role to play as pain-relieving options in patients who are unable to tolerate other classes of drugs or have demonstrated lack to efficacy in response to, for example, NSAIDs and/or opiate drugs.

Findings from several large international studies suggest that the correlation between pain and structural change may not be a linear, particularly in a chronic disease, such as OA, when flares may occur (Figure 5). Emerging studies suggest that newer techniques such as quantitative sensory testing and brain neuroimaging may help to further phenotype pain subgroups in OA, which could help to develop pathways for the treatment of OA pain in the future. If it is accepted that pain sensitization is influenced by both physical factors occurring in the joint and psychological influences on pain, then it could be argued that an early combined approach of both pharmacotherapy plus other interventions, such as pain management programs, to inhibit the development of sensitization, for example, before chronic pain develops, could have an effect on clinical pain. Such interventions, early in the disease process, may be effective in modulating the development of chronic pain in OA, but will need to be tested in the context of clinical trials.

Conclusion

OA is a heterogeneous and debilitating disorder for which there are no universally accepted disease-modifying treatments. It affects large weight-bearing joints including the hip and knee but also smaller joints often in a nodal distribution in the hands. Recognized risk factors include obesity, genetic risk and previous mechanical injury. Since OA is a chronic disease that often progresses after the third or fourth decades, any intervention for pain that is used needs to be safe, with minimal side effects and of long-term benefit. It is interesting to note that many of the agents discussed in this review that could have a therapeutic effect, are also associated with potential harmful effects. For example, NSAIDs, such as indomethacin, can lead to destruction of cartilage, as can treatment with anti-NGF and corticosteroid therapy, suggesting that a positive effect on joint pain may also be associated with accelerated joint destruction, which is an extremely important factor in a chronic, long-term condition such as OA. Recent work highlighted in this review also suggests that the relation between pain and structural damage does not always follow a linear pattern in OA (Figure 5). Recent focus has been on optimizing efficacy of analgesics including NSAIDs and opiates. Emerging data from meta-analyses suggests a limited role for nutraceuticals including glucosamine and chondroitin. The physician looking after OA patients may need to consider the use of centrally acting analgesics, such as duloxetine, if there is lack of efficacy with NSAID/opiates over time and possibly clinical evidence of sensitization. It is only when risk factor reduction, lifestyle advice and pharmacological intervention have been

unsuccessful that joint replacement surgery can be considered primarily for OA of the hip and knee.

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Int J

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New Trends in Pharmacological Treatments for Osteoarthritis

Osteoarthritis (OA) is the leading cause of function loss and disability among the elderly, with significant burden on the individual and society. It is a severe disease for its high disability rates, morbidity, costs, and increased mortality. Multifactorial etiologies contribute to the occurrence and development of OA. The heterogeneous condition poses a challenge for the development of effective treatment for OA; however, emerging treatments are promising to bring benefits for OA management in the future. This narrative review will discuss recent developments of agents for the treatment of OA, including potential disease-modifying osteoarthritis drugs (DMOADs) and novel therapeutics for pain relief. This review will focus more on drugs that have been in clinical trials, as well as attractive drugs with potential applications in preclinical research. In the past few years, it has been realized that a complex interaction of multifactorial mechanisms is involved in the pathophysiology of OA. The authors believe there is no miracle therapeutic strategy fitting for all patients. OA phenotyping would be helpful for therapy selection. A variety of potential therapeutics targeting inflammation mechanisms, cellular senescence, cartilage metabolism, subchondral bone remodeling, and the peripheral nociceptive pathways are expected to reshape the landscape of OA treatment over the next few years. Precise randomized controlled trials (RCTs) are expected to identify the safety and efficacy of novel therapies targeting specific mechanisms in OA patients with specific phenotypes.

Keywords: osteoarthritis, novel therapeutics, DMOADs, therapy selection, clinical prospect

INTRODUCTION

Osteoarthritis (OA) can be viewed as the structural and functional failure of the synovial joint organ (Loeser et al., 2012). All tissues of the joint can be involved, including articular cartilage, subchondral bone, and synovium (Felson, 2006). OA is the leading cause of function loss and disability among elderly, which makes these patients suffer from chronic pain (Hunter and Bierma-Zeinstra, 2019). Traditionally the management of OA has been constrained to symptom relieving (Arden et al., 2020); the non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics are most commonly applied to OA for relieving pain, however, their side-effects often restrict their use (Bally et al., 2017; da Costaet al., 2017; Fuggle et al., 2019; Leopoldino et al., 2019). In recent years, there has been substantial progress made in understanding the pathogenesis of OA.

OA is a very complicated pathophysiologic process and is a result of interacting action of multiple mechanisms. Mechanical overload, genetic alterations, sex hormone deficiency, aging, metabolic imbalance and low-grade chronic inflammation all may contribute to the imbalance between catabolism and anabolism of joint tissues, and lead to eventual joint damage in OA. The etiological heterogeneity causes a great difficulty on the development of an effective treatment for OA. The development of OA is a very complicated pathophysiologic process and is a result of interaction of multiple mechanisms. Mechanical overload, genetic alterations, sex hormone deficiency, aging, metabolic imbalance and low-grade chronic inflammation all may contribute to the imbalance between catabolism and anabolism of joint tissues and lead to eventual joint damage in OA (Chen D. et al., 2017; Oo et al., 2018). The etiological heterogeneity causes a great difficulty on the development of an effective treatment for OA. Epidemiological data support significant associations between structural changes and longterm outcome. However, the available therapeutic regimens of OA are merely symptom-relieving drugs unable to modify the progression of OA and to prevent long-term disability, and the symptom-structure discordance is well-recognized in clinical course of OA. Thus, the guidelines from the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) point out that the effective diseasemodifying osteoarthritis drugs (DMOADs) should be developed (Reginster et al., 2015; Oo et al., 2018). A DMOAD is expected a drug that modifies the underlying OA pathophysiology, thereby inhibiting structural damage to prevent or reduce long-term disability and offer potential symptomatic relief (Latourte et al., 2020). Currently, there are no US FDA- or EMAapproved DMOADs. But emerging treatments targeting inflammation, cartilage metabolism, and subchondral bone remodeling, which may retard the structural progression and induce disease remission, are promising to bring benefits to OA management in the future.

This narrative review will discuss recent developments of agents for the treatment of OA, including potential DMOADs and novel therapeutics for pain relief (Table 1). This review will focus more on drugs that have been in clinical trials, as well as attractive drugs with potential applications in preclinical research, to provide clinicians with recent advances in OA pharmacological therapies.

Investigational drugs targeting Inflammatory mechanisms

The inflammatory mediators can be detected in both synovial fluid and serum in OA patients, indicating that inflammation does play a significant role in the pathogenesis of OA (LeGrand

TABLE 1 | Major emerging drugs to control structural damage and relieve pain in OA clinical trials.

Type of drug	Route of administration	Major findings	Stage of development	Clinical trials. gov identifier
Targeting inflammatory mechanisms				
IL-1 inhibitors				
Anakinra	Intra-articular	Anakinra did not significantly improve symptoms in patients with knee OA.	Phase II (knee OA)	NCT00110916
AMG 108	Subcutaneous/Intra-articular	AMG 108 showed statistically insignificant but numerically greater improvements in pain.	Phase II (knee OA)	NCT00110942
Canakinumab	Intra-articular	The clinical trial was completed, but the results have not been published.	Phase II (knee OA)	NCT01160822
Gevokizumab	Subcutaneous	The clinical trials were completed, but the results have not been published.	Phase II (erosive hand OA) Phase II (erosive hand OA)	NCT01683396 NCT01882491
Lutikizumab (ABT-981)	Subcutaneous	Lutikizumab was generally well tolerated in patients with knee OA and elicited an anti-inflammatory response.	Phase I (knee OA)	NCT01668511
		Lutikizumab did not improve pain or imaging outcomes in erosive hand OA compared with placebo.	Phase IIa (erosive hand OA)	NCT02384538
		Lutikizumab was not an effective analgesic/anti-inflammatory therapy in most patients with knee OA associated synovitis.	Phase IIa (knee OA)	NCT02087904 (ILL-USTRATE- K trail)
TNF- α inhibitors				
Etanercept	Subcutaneous	Subcutaneous injection of Etanercept for 24 weeks did not relieve pain effectively in patients with erosive hand OA compared with placebo.	—	NTR1192 (EHOA trail)
Infliximab	Intra-articular	Treatment with Infliximab can reduce the incidence of secondary OA in proximal interphalangeal joints in patients with active RA.	Exploratory observational longitudinal study	—
		Infliximab was safe, and significantly improved pain symptoms	Plot study (erosive hand OA)	—
Adalimumab	Subcutaneous	Adalimumab was not superior to placebo in relieving pain in patients with erosive hand OA.	Phase III (erosive hand OA)	NCT00597623
		Adalimumab did not affect synovitis or BMLs in patients with hand OA with MRI-detected synovitis.	—	ACTRN12612000791831 (HUMOR trial)
		Adalimumab significantly slowed the progression ofjoint aggressive lesions in a subpopulation with palpable tissue swelling of the interphalangeal joints.	—	EudraCT 2006 –000925 –71
DMARDs				
HCQ	Oral	HCQ did not relieve symptoms or delay structural damage.	—	ISRCTN91859104 (HERO trial)
MTX	Oral	MTX significantly reduced pain and improved synovitis in patients with symptomatic knee OA.	—	NCT01927484
		MTX added to usual care demonstrated significant reduction in knee OA pain at 6 months, and significant improvements in WOMAC stiffness and function. No effect on synovitis	Phase III (knee OA)	ISRCTN77854383 (PROMOTE trial)
		The clinical trial is ongoing	—	NCT03815448
Removing SnCs				
UBX0101	Intra-articular	The clinical trials were completed, but the results have not been published.	Phase I (knee OA) Phase I (knee OA) Phase II (knee OA)	NCT03513016 NCT04229225 NCT04129944
Curcuma longa extract	Oral	Curcuma longa extract was more effective than placebo for knee pain but did not affect knee effusion-synovitis or cartilage composition.	Phase II (knee OA)	ACTRN12618000080224
		The clinical trial is ongoing	Phase III (hip or knee pain)	NCT04500210
Targeting Cartilage Metabolism				
Wnt pathway inhibitors				
Lorecivivint (SM04690)	Intra-articular	Lorecivivint 0.07 mg was superior to the placebo in improving pain and function, and increased the JSW in patients with knee OA.	Phase I (knee OA)	NCT02095548
		Lorecivivint had no signnficant effects in knee OA patients, but significantly relieved pain, improved joint function, and increased JSW in a subgroup of patients (patients with unilateral symptomatic knee OA and unilateral symptomatic knee OA without extensive pain).	Phase IIa (knee OA)	NCT02536833
		The clinical trial is ongoing	Phase III (knee OA)	NCT03928184
Cathepsin-K inhibitors				
MIV-711	Oral	MIV-711 was not more effective than placebo for pain, but it significantly reduced bone and cartilage progression with a reassuring safety profile.	Phase a (knee OA)	NCT02705625

(Continued on following page)

TABLE 1 | (Continued) Major emerging drugs to control structural damage and relieve pain in OA clinical trials.

Type of drug AGG-523	Route of administration	Major findings	Stage of development	Clinical trials. gov identifier
MMP/ADAMTS inhibitors				
	Oral	The clinical trials were completed, but the results have not been published	Phase I (knee OA)	NCT00454298
			Phase I (knee OA)	NCT00427687
M6495	Subcutaneous	The clinical trial was completed, but the results have not been published.	Phase Ib (knee OA)	NCT03583346
Growth factors				
Sprifermin (rhFGF18)	Intra-articular	Sprifermin appeared safe and well-tolerated, and it showed a statistically significant dose-dependent effect in reducing the loss of total and lateral femorotibial cartilage thickness and loss oflateral radiographic JSW.	Phase I (knee OA)	NCT01033994
		Sprifermin had a limited effect on pain improvement, but had a statistically significant effect in reducing the loss of total femorotibial cartilage thickness.	Phase II (knee OA)	NCT01919164 (FO-RWARD trial)
GEC-TGF-β1	Intra-articular	GEC-TGF- β1 significantly improved pain function and physical ability.	Phase II (knee OA)	NCT01221441
			Phase II (knee OA)	NCT01671072
		GEC-TGF- β1 had beneficial effects on pain and functional improvement in patients with OA, but had limited effects on structural improvement.	Phase III (knee OA)	NCT02072070
Activating AMPK pathway				
Metformin	Oral	Metformin may have a beneficial effect on long-term knee joint outcomes in those with knee OA and obesity.	Prospective cohort study (knee OA)	—
Targeting the Subchondral Bone				
Bisphosphonate				
Zoledronic Acid	Intra-articular	Zoledronic acid did not significantly reduce cartilage volume loss, relieve pain, or improve BMLs.	Phase (Knee OA)	ACTRN12613000039785
Calcitonin				
Salmon calcitonin	Oral	Salmon calcitonin did not improve pain symptoms and JSW in patients with symptomatic knee OA.	Phase (Knee OA)	NCT00486434
				NCT00704847
Strontium Ranelate	Oral	Strontium Ranelate significantly inhibited the narrowing of the medial femoral joint space, relieved pain, and improved physical function in patients with moderate to severe knee OA.	Phase (Knee OA)	ISRCTN41323372 (SEKOIA trial
Teriparatide	Subcutaneous	The clinical trial is ongoing.	Phase (knee OA)	NCT03072147
Vitamin D	Oral	Vitamin D supplementation, compared with placebo, did not result in significant differences in change in MRI-measured tibial cartilage volume or WOMAC knee pain score over 2 years, but might have beneficial effects on physical function, foot pain, depressive symptoms and effusion-synovitis.	Phase (Knee OA)	NCT01176344
Investigational Drugs to relieve pain				
NGF inhibitors				
Tanezumab	Subcutaneous	Tanezumab was significantly better than the placebo in improving pain and physical function, and PGA-OA.	Phase III (hip or knee OA)	NCT02697773
		Tanezumab statistically significantly improved pain, physical function and PGA-OA in patients with moderate to severe OA who had not responded to or could not tolerate standard-of-care analgesics	Phase III (hip or knee OA)	NCT02709486
Fasinumab	Subcutaneous	Fasinumab significantly improved pain and function in patients with OA, even in those who obtained little benefit from previous analgesics	Phase IIb/III (hip or knee OA)	NCT02447276
		The clinical trials are ongoing	Phase III (hip or knee OA)	NCT02683239 NCT03285646 NCT03161093 NCT03304379
Triamcinolone acetonide sustained-release agent				
Zilretta (FX006)	Intra-articular	Zilretta significantly reduced ADP-intensity compared with saline-solution placebo. Zilretta significantly improved pain, stiffness, physical function, and the quality oflife compared with both placebo and TAcs	Phase III (knee OA)	NCT02357459

OA: osteoarthritis; RA: rheumatoid arthritis; BMLs: bone marrow lesions; DMARDs: disease-modifying antirheumatic drugs; HCQ: hydroxychloroquine; MTX: methotrexate; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SnCs: senescent cells; JSW: joint space width; MMP: matrix metalloproteinase; ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs; rhFGF18: recombinant humanfibroblast growth factor 18; NGF: nerve growth factor; PGA-OA: patient's Global assessment of OA; ADP: average-daily-pain; TAcs: triamcinolone acetonide crystal suspensions.

Key points

- **OA as Inflammatory:** Osteoarthritis is recognized as a low-grade inflammatory disease linked to immune dysregulation from aging.
- **IL-1 Inhibitors:** IL-1 inhibitors like Anakinra and AMG 108 are tolerable but show limited symptom improvement in OA.
- **Canakinumab's Promise:** Canakinumab reduces OA symptoms and cartilage destruction, with protective effects on chondrocytes in preclinical studies.
- **Lutikizumab's Outcomes:** Lutikizumab, targeting IL-1**α** and IL-1**β**, is safe but has shown disappointing results in phase II trials for pain and joint structure.

et al., 2001). OA is now seen as a low-grade inflammatory disease compared to rheumatoid arthritis (RA) (Scanzello and Loeser, 2015). Recently, studies have revealed that the low-grade, chronic, sterile inflammation associated with OA is closely related to dysregulation of the immune system as aging (Millerand et al., 2019). Anti-inflammatory therapeutics and treatment modalities targeting senescence processes may be promising approaches to attenuate disease progression of OA.

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Interleukin (IL)-1 Inhibitors

IL-1 has an increased expression in cartlage, synovium, and synovial fluid in OA patients (Sohn et al., 2012). It is an important proinflammatory cytokine and pain mediator resulting in pain sensitization, bone resorption, and cartilage destruction. Thus, IL-1 inhibitors may protect against structural changes in OA (Miller et al., 2014; Schett et al., 2016). Cytokines of the IL-1 family members include IL-1**α**, IL-1**β**, and endogenous IL-1 receptor antagonist (IL-1Ra). The ideal treatment is to effectively inhibit IL-1**α** and IL-1**β** without interfering with IL-1Ra.

1) Drugs targeting IL-1 receptor include human IL-1 receptor antagonist Anakinra, and human IL-1 receptor type 1 (IL-1R1) monoclonal antibody AMG 108 produced by genetic recombination technology. In two randomized, double-blind, placebo-controlled studies, it was found that subcutaneous (SC) or intravenous (IV) of AMG 108 and a single intra-articular (IA) injection of Anakinra were well tolerated (Chevalier et al., 2009; Cohen et al., 2011). Patients in the study received SC or IV injection of AMG 108 every 4 weeks for 12 weeks, and the results showed that patients who received AMG 108 showed statistically insignificant but numerically greater improvements in pain compared to placebo (Cohen et al., 2011). Similarly, IA injection of Anakinra did not significantly improve symptoms in patients with knee OA (Chevalier et al., 2009). Neither of these studies evaluated the effects on the joint structure.

2) Drugs targeting IL-1**β** include the humanized monoclonal antibody Canakinumab and the IL-1**β** allosteric modulating antibody Gevokizumab, which inhibit IL-1**β** receptor activation by tightly binding IL-1**β**. Canakinumab is considered as a disease-modifying antirheumatic drug (DMARD), has been shown to improve symptoms of juvenile idiopathic arthritis and RA, and decrease cartilage destruction (Sota et al., 2018). A recent preclinical study demonstrated that Canakinumab had protective effects on human OA chondrocytes in vitro (Cheleschi et al., 2015). In the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS trial), it was observed that Canakinumab reduced not only cardiovascular events but also the incidence of total knee or hip replacement as a result of OA (Chevalier and Eymard, 2019). A phase II study (NCT01160822) on the safety, tolerability, pharmacokinetics, and pain effects of a single IA injection of Canakinumab in patients with knee OA was completed, but the results have not been published. Another phase II studies (NCT01683396; NCT01882491) to test the safety and biologic activity of Gevokizumab, and an open-label safety extension study of Gevokizumab (NCT02293564) in patients with hand OA were completed, but no published results are available.

3) Lutikizumab (formerly ABT-981) is a human dual variable domain immunoglobulin (DVD-Ig), simultaneously binding and inhibiting IL-1**α** and IL-1**β** (Lacy et al., 2015). In a randomized placebo-controlled phase I study, Lutikizumab was generally well tolerated in patients with mild to moderate knee OA, and significantly reduced serum concentrations of matrix metalloproteinase (MMP)-1 and high-sensitivity C-reactive protein (hsCRP) (Wang S. X. et al., 2017). However, the results from two recent phase II clinical studies to assess the efficacy of Lutikizumab in patients with hand OA and knee OA were unsatisfactory (Fleischmann et al., 2019; Kloppenburg et al., 2019). In erosive hand OA, Lutikizumab was administrated subcutaneously every 2 weeks for 26 weeks, but there were no significant differences in pain score, and in changes of X-ray or magnetic resonance imaging (MRI) scores between Lutikizumab and place-

bo (Kloppenburg et al., 2019). In knee OA with evidence of synovitis (ILLUSTRATE-K trial), Lutikizumab was administrated subcutaneously with three different doses (25, 100, and 200 mg) every 2 weeks for 50 weeks, the results showed that only lutikizumab 100 mg was slightly superior to the placebo in pain improvement at week 16 (Fleischmann et al., 2019). Moreover, at weeks 26 and 52, there were no significant differences between the lutikizumab and placebo groups in MRI-detected synovitis, radiographic medial and lateral joint space narrowing (JSN), and cartilage thickness (Fleischmann et al., 2019). These results suggest that IL-1 inhibition is not effective in most patients with OA. Whether subgroups of OA patients might have symptomatic or disease-modifying benefits from IL-1 inhibition remains an open question.

Tumor Necrosis Factor-Alpha Inhibitors

TNF-**α**, a proinflammatory cytokine produced by synoviocytes and chondrocytes in OA, plays a central role in the induction of structural damage and pain modulation in OA. Besides, TNF-**α** enhances the production of a series of other proinflammatory cytokines (such as IL-6 and IL-8), stimulates the synthesis of MMP and cyclooxygenase (COX), and increases NO production (Orita et al., 2011). Preclinical studies suggested that anti-TNF-**α** therapy might exert a protective effect on articular cartilage by improving the structure of the subchondral bone and reducing cartilage matrix degradation (Ma et al., 2015). Thus, inhibitors of TNF-**α** might be considered as potential candidates for diseasemodifying therapy in OA.

(1) Etanercept is a recombinant human tumor necrosis factor receptor type II antibody fusion protein. A study investigated the effect of IA injection of Etanercept for pain in moderate and severe knee OA. The results showed that compared with the hyaluronic acid group, direct injection of Etanercept into OA knee joints could effectively relieve the pain symptoms in OA patients (Ohtori et al., 2015). However, A recent randomized, double-blind, placebo-controlled trial (EHOA trial) found that the SC injection of Etanercept for 24 weeks did not relieve pain effectively in patients with erosive hand OA compared with placebo (Kloppenburg et al., 2018). In subgroup analysis, joints treated with Etanercept for 52 weeks showed more radiographic remodeling and less MRI bone marrow lesions (BMLs), which was more pronounced in actively inflamed joints at the baseline (Kloppenburg et al., 2018). In this study, Etanercept was observed to reduce serum levels of MMP-3, an important mediator of joint destruction (Kroon et al., 2020). Overall, this study did not provide evidence for the use of Etanercept to treat hand OA, but from a therapeutic strategy targeting inflammation, the authors believed that short-term treatment with TNF-**α** inhibitors during disease flares could be considered.
(2) Infliximab is a human/mouse chimeric monoclonal antibody of immunoglobulin G (IgG) 1/k subtype (composed of human IgG1 constant region and murine variable region). An exploratory observational longitudinal study found that treatment with Infliximab can reduce the incidence of secondary OA in proximal interphalangeal joints in patients with active RA (Guler- Yuksel et al., 2010). A pilot study investigated the efficacy and tolerability of IA injection of Infliximab in erosive hand OA (Fioravanti et al., 2009). The results showed that IA injection of Infliximab was safe, and significantly improved pain symptoms. Infliximab tended to reduce radiological scores of anatomical lesions in the hand, but the difference did not reach statistical significance. The study suggested a possible symptom- and disease alleviating effect of Infliximab, but clinical trials are still needed to elucidate the true effect of Infliximab in OA.
(3) Adalimumab is the first bioengineered fully human monoclonal antibody that binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with both Types 1 and 2 TNF receptors (TNFR1 and -R2). A 12-month, double-blind, randomized controlled trial evaluated the efficacy and safety of Adalimumab in controlling structural damage in patients with erosive hand OA (Verbruggen et al., 2012). The tolerability and safety of Adalimumab in patients with erosive hand OA were similar to those in patients with other systemic rheumatic diseases. Compared with placebo, Adalimumab did not halt the progression of joint damage in overall patients, but it significantly slowed the progression of joint aggressive lesions in a subpopulation with palpable tissue swelling of the interphalangeal joints. However, in two randomized double-blind placebo-controlled trials, Adalimumab was not superior to placebo in relieving pain in patients with

Key points

- **IL-1 Inhibition:** Targeting IL-1**α** and IL-1**β** shows limited efficacy in improving symptoms and disease progression in OA, with treatments like Anakinra, Canakinumab, and Lutikizumab lacking significant benefits in clinical trials.
- **Canakinumab's Promise:** This monoclonal antibody demonstrated protective effects on OA chondrocytes and reduced the need for joint replacements, indicating potential benefits in specific patient populations.
- **TNF-α Role:** TNF-**α** inhibitors, including Etanercept, Infliximab, and Adalimumab, aim to mitigate structural damage in OA, but results vary, with Etanercept showing limited effectiveness in erosive hand OA.
- **Clinical Trials Needed:** Overall, both IL-1 and TNF-**α** inhibitors require further investigation to clarify their roles and potential benefits in managing OA effectively.

Key points

- **HCQ Ineffective:** Hydroxychloroquine failed to reduce symptoms or structural damage in hand OA across multiple trials, including the HERO trial.
- **MTX Shows Promise:** Methotrexate provided pain relief and reduced synovitis in knee OA, but did not affect synovial volume; further research is ongoing.
- **Senescent Cells Targeted:** UBX0101 targets senescent cells, showing potential in early trials for OA, with results from ongoing studies pending.
- **Curcumin Benefits:** Curcumin from Curcuma Longa may relieve knee pain and enhance quality of life, though effects on synovitis and cartilage are unclear.

erosive hand OA (Chevalier et al., 2015; Aitken et al., 2018), and one study (HUMOR trial) also indicated that Adalimumab did not affect synovitis or BML in patients with hand OA with MRI-detected synovitis (Aitken et al., 2018).

DMARDs

With the increasing acceptance of the inflammatory phenotype of OA, traditional DMARDs may have the potential to reduce pain and slow structural degeneration in OA. Hydroxychloroquine (HCQ) has been successfully used in the treatment of mild RA and other autoimmune diseases for many years (Ghouri and Conaghan, 2019). A randomized trial during 24 weeks showed that compared with placebo, HCQ was not effective in reducing the symptoms of hand OA (Lee et al., 2018). Recently, a randomized double-blind placebo-controlled trial (HERO trial) with 12-month follow-up evaluated the efficacy of HCQ in hand OA patients with moderate to severe pain, and the results showed that HCQ did not relieve symptoms or delay structural damage (Kingsbury et al., 2018).

Methotrexate (MTX) is a traditional DMARD for the treatment of some autoimmune diseases such as RA. The study (NCT01927484) reported that oral MTX significantly relieved pain and reversed features of synovitis in patients with symptomatic knee OA, which indicated MTX as an option for the treatment of knee OA (Abou-Raya et al., 2018). A pragmatic phase III RCT was completed (PROMOTE trial) to determine whether oral MTX reduced pain and synovitis associated with knee OA in 2019 (Kingsbury et al., 2015). The results presented at Osteoarthritis Research Society International (OARSI) Annual Congress showed that MTX significantly reduced knee OA pain, and significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for stiffness and function. However, MTX did not change the synovial volume assessed by MRI in this study. Meanwhile, a multicenter RCT study to investigate the effect of oral MTX on pain and synovitis in patients with mid-to late-stage knee OA (NCT03815448) is ongoing (Zhu et al., 2020), and further data are expected to come soon. Overall, more evidence is needed to clearly define the role of MTX in OA treatment.

Targeting Senescent Cells

The innate immune activation caused by the dysregulation of the immune system with aging is considered to play a crucial role in the chronic inflammation of OA (Jeon et al., 2018). Age-related mitochondrial dysfunction and associated oxidative stress might induce senescence in joint tissue cells (Coryell et al., 2020). The accumulation of SnCs in joints causes the secretion of proinflammatory and pro-catabolic factors (cytokines, chemokines, MMPs), which is called a "senescence-associated secretory phenotype" (SASP) (Childs et al., 2017; Millerand et al., 2019). Direct targeting the SnCs provides a potential opportunity to eliminate the source of OA disease (Childs et al., 2017; Jeon et al., 2017). UBX0101 is a small molecule lysosomal agent that can reduce the expression of SASP factors and improve overall joint function (Jeon et al., 2017). Currently, several randomized, placebo-controlled clinical trials of UBX0101 are all completed in 2020 to evaluate the efficacy, safety, and tolerability of IA injection of UBX0101 in knee OA patients (NCT03513016, NCT04229225, and NCT04129944), and the results will be released soon.

Curcuma Longa Extract

Curcuminoids, are the principal extracted from the CL root (Family Zingiberaceae), which comprise curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) (Cao et al., 2014). The curcumin is the main active and effective ingredient. Curcumin is known to suppress oxidative stress and inflammation by scavenging active oxygen and inhibiting nuclear factor-kappa **β** (NF-**κβ**) pathway (Shen and Ji, 2012; Wang J. et al., 2017). A systematic review and meta-analysis of RCT enrolled 797 patients with primarily knee OA demonstrated that Curcuminoids had some beneficial effects on knee pain and quality of life in patients with knee OA (Onakpoya et al., 2017). Recently, a single-center, randomized, placebo controlled trial with 12-week follow-up evaluated the efficacy of CL in patients with symptomatic knee OA and effusion-synovitis, and the results showed that CL was superior to placebo in relieving knee pain but did not affect the effusion-synovitis volume or cartilage composition as assessed by MRI (Wang et al., 2020). However, the follow-up time was relatively short so that

it might be insufficient to detect a change in the cartilage- and synovium-specific outcomes in this study. Another double-blind, randomized, parallel-group, phase III comparative study (NCT04500210) of CL and placebo to patients with mild to moderate OA of the knee and or hip is still recruiting. Further researches with larger sample sizes are needed to assess the clinical significance of CL in OA treatment.

Investigational drugs targeting Cartilage metabolism

The characteristic sign of OA is cartilage destruction, so emerging drugs targeting the molecular mechanism of articular cartilage should be an attractive therapeutic strategy for OA. The research direction is mainly to delay cartilage destruction by anti-catabolic agents and stimulate cartilage development and repair by anabolic agents.

Wnt Signaling Pathway Inhibitors

The balance of Wnt pathway activity is integral for regulating the differentiation of progenitor cells in the joint and maintaining cartilage homeostasis (Lories et al., 2013; Thysen et al., 2015). In OA, aberrant Wnt pathway activity leads to the differentiation of progenitor cells into osteoblasts while chondrocyte development is blocked, as well as the increased secretion of catabolic enzymes and inflammation.

Preclinical studies demonstrated that Wnt pathway inhibitors could delay the development of OA in animal models; however, excessive inhibition, in turn, caused cartilage and bone destruction. Thus, targeting the Wnt pathway and controlling it within an optimal range is a potential therapeutic avenue (Usami et al., 2016; Deshmukh et al., 2018).

Lorecivivint (formerly SM04690) is a small-molecule Wnt pathway inhibitor and modulates the Wnt pathway by inhibiting two intranuclear targets, intranuclear kinases CDClike kinase 2 (CLK2) and dual-specificity tyrosine phosphorylation-regulated kinase 1 A (DYRK1A) (Deshmukh et al., 2019). In a 24-week, randomized, placebo-controlled phase I study, a single IA injection of Lorecivivint (0.03, 0.07, or 0.23 mg) appeared safe and well-tolerated (Yazici et al., 2017). Lorecivivint 0.07 mg was superior to the placebo in improving WOMAC pain scores and function scores in patients with moderate to severe knee OA, while the 0.07 mg dose group also showed an increase from baseline in radiographic joint space width (JSW) (Yazici et al., 2017).

Recently, the results of a 52-week multicenter, randomized, double-blind, placebo-controlled phase IIa study announced that Lorecivivint treatment was not superior to placebo for improving pain, joint function, and radiographic JSW in patients with moderate to severe knee OA (Deshmukh et al., 2019), but in subgroup patients with unilateral symptomatic knee OA or unilateral symptomatic knee OA without extensive pain, Lorecivivint 0.07 mg significantly relieved pain, improved joint function, and increased JSW compared with placebo (Deshmukh et al., 2019). The study suggested that Lorecivivint might be effective in OA patients with a certain phenotype.

Besides, a phase III clinical study (NCT03928184) has been initiated in 2019 to assess the long-term efficacy and safety of Lorecivivint in the treatment of knee OA, and Lorecivivint has the potential to be an effective treatment for OA.

Cathepsin-K Inhibitors

Cathepsin-K is the predominant cysteine cathepsin in the skeleton and it plays an important role in the resorption of cartilage and bone (Dejica et al., 2008). Several observations have demonstrated up-regulation of cathepsin K in OA cartilage and inflamed synovial tissue (Salminen-Mankonen et al., 2007). Cathepsin-K may be an attractive therapeutic target for diseases with excessive bone resorption such as osteoporosis and OA. Cathepsin K inhibitors have shown structural protection and analgesic effects in animal models of joint degeneration (Lindström et al., 2018a; Nwosu et al., 2018).

The results of phase II clinical study evaluating the efficacy and safety of the Cathepsin-K inhibitor Balicatib in OP and OA patients showed that it could improve bone mineral density in OP patients, but it failed to decrease cartilage volume loss (CVL) in patients with knee OA (Duong et al., 2016). Also, Balicatib could lead to dose-related

Key points

- **Curcuma Longa:** Further research is needed on Curcuma Longa extract (CL) for OA, with ongoing phase III studies.
- **Cartilage Metabolism Targets:** New therapies aim to slow cartilage destruction and promote repair, focusing on Wnt pathway inhibitors like Lorecivivint.
- **Lorecivivint Results:** Initial benefits for specific OA phenotypes were noted, but larger trials showed no significant overall improvement.
- **Cathepsin-K Inhibitors:** Cathepsin-K is a potential OA target, but trials, including Balicatib, have not consistently shown effectiveness in reducing cartilage loss.

Key points

- **MIV-711:** Selective cathepsin K inhibitor; protects cartilage and bone but didn't significantly reduce knee pain in phase IIa study.
- **MMP/ADAMTS Inhibitors:** Targeting MMPs and ADAMTS enzymes shows potential in slowing OA progression; selective MMP-13 inhibitors and ADAMTS-5 drugs show promise in preclinical trials.
- **Growth Factors:** Sprifermin (rh-FGF18) promotes cartilage repair; initial trials were safe but not superior to placebo in reducing cartilage loss. Further validation needed.

adverse effects-Morphea-like skin reactions (Runger et al., 2012).

MIV-711 is a highly selective cathepsin K inhibitor that has been shown in preclinical animal models of OA to reduce cartilage lesions, reduce levels of biomarkers reflecting the degradation of bone and cartilage [carboxy-terminal collagen cross links (CTX)-I and CTX-II] and prevent subchondral bone loss (Lindström et al., 2018a; Lindström et al., 2018b). A recent randomized, double-blind, placebo-controlled phase IIa study to assess the efficacy and safety of MIV-711 in symptomatic patients with Kellgren-Lawrence (KL) grade 2 and 3 knee OA (Conaghan et al., 2020). The results showed that oral administration of MIV-711 (100 mg/d or 200 mg/d) for 26 weeks had a significant protective effect on both bone and cartilage structures, and significantly reduced the levels of CTX-I and CTX-II, but failed to meet the primary study endpoint of alleviating knee joint pain (Conaghan et al., 2020). MIV-711 has a good safety profile, but its clinical efficacy remains to be validated in longer-term and larger-scale clinical studies.

MMP/ADAMTS Inhibitors

Aggrecan and type II collagen are two main components of articular cartilage, which are essential for maintaining the function and integrity of cartilage (Malfait and Tortorella, 2019). Aggrecan provides the compressibility of cartilage, while collagen provides its elasticity. These macromolecules are decomposed by proteolysis. MMPs and aggrecanase (a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), mainly ADAMTS-4 and ADAMTS-5) are demonstrated to have critical roles in the degradation of type II collagen and aggrecan, respectively, and are considered as potential targets for OA treatment.

(1) In preclinical trials, highly selective MMP-13 inhibitors (such as ALS1-0635 and PF152) have shown advantages in slowing the progression of OA (Piecha et al., 2010; Schnute et al., 2010). However, the available data on the role of MMP-13 inhibitors in OA treatment is limited, and human clinical trials are still needed to observe the efficacy of MMP-13 inhibitors as DMOADs.
(2) At present, the investigational drugs targeting ADAMTS- 5/ADAMTS-4 include a chimeric murine/human ADAMTS-5 monoclonal antibody-CRB0017, which was reported to slow OA disease progression after IA administration in animal models of OA (Chiusaroli et al., 2013), and a humanized ADAMTS-5-selective monoclonal antibody, GSK2394002, which was reported to have structural modification and analgesic effects in animal models of OA (Larkin et al., 2015; Miller et al., 2016). AGG-523, an orally small molecule inhibitor of ADAMTS-4 and ADAMTS-5, was the first to enter the human phase I study (NCT00454298 and NCT00427687), but these trials were discontinued for unknown reasons. M6495, a novel anti-ADAMTS-5 inhibiting Nanobody, showed dose-dependent protection against cartilage deterioration in ex vivo cartilage cultures (Siebuhr et al., 2020). A phase Ib (NCT03583346) clinical trial to assess safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of SC injections of M6495 in knee OA patients was completed in 2019, but the results have not yet been published.

Growth Factors

Different from using anti-catabolic agents to delay the progression of cartilage destruction, an alternative approach is to stimulate the growth and repair of cartilage for the treatment of OA. Several growth factors have been shown to stimulate cartilage anabolism and promote cartilage repair in vitro and animal models of OA. Growth factors may have potential therapeutic effects on OA.

(1) Sprifermin is a recombinant human fibroblast growth factor 18 (rhFGF18) (Onuora, 2014), and preclinical data had shown that Sprifermin bound to and activated fibroblast growth factor receptor 3 (FGFR3) in cartilage to promote chondrogenesis, cartilage matrix formation, and cartilage repair in vivo and in vitro (Moore et al., 2005; Gigout et al., 2017; Reker et al., 2017; Sennett et al., 2018). A randomized, double-blind, placebo-controlled phase I b proof-of-concept trial evaluated the efficacy and safety of IA injection of Sprifermin (10, 30, and 100 μg) in patients with symptomatic knee OA (Lohmander et al., 2014). The results showed that Sprifermin appeared safe and welltolerated. Although Sprifermin was not superior to placebo in reducing the loss of central medial femorotibial compartment

(cMFTC) cartilage thickness and improving pain, it showed a statistically significant dose-dependent effect in reducing the loss of total and lateral femorotibial cartilage thickness and loss of lateral radiographic JSW (Lohmander et al., 2014). Two posthoc analyses of this study demonstrated that Sprifermin (100 µg) reduced cartilage loss, increased cartilage thickness, and improved BMLs (Eckstein et al., 2015; Roemer et al., 2016).

A 5-years, dose-finding, multicenter phase II clinical trial (FORWARD trial), published in 2019, showed that IA injection of 100 µg Sprifermin every 6 or 12 months significantly increased the total femorotibial joint cartilage thickness in patients with symptomatic knee OA after 2 years, and this effect was dose-dependent. Sprifermin had a limited effect on pain improvement in this study (Hochberg et al., 2019). Recently, two post-hoc exploratory analyses were carried out on this study, and the results showed that sprifermin treatment could significantly increase cartilage thickness and reduce cartilage loss, making cartilage loss in patients with knee OA similar to that of healthy subjects (Brett et al., 2020; Eckstein et al., 2020). The above studies supported the conclusions that sprifermin modified structural progression and could be a potential DMOAD.

(2) Transforming growth factor-**β**1 (TGF-**β**1) plays an important role in the development and maturation of articular cartilage and the phenotypic maintenance of chondrocytes (Yang et al., 2001; Crane et al., 2016). The expression of TGF-**β**1 in healthy cartilage is significantly higher than that in OA cartilage; however, it has been found that overexpression of TGF-**β**1 leads to OA-like changes in the knee joint of C57Bl/6 mice, including hyperplasia of the synovium and osteophyte formation (Bakker et al., 2001). Recently, Liu et al. demonstrated that TGF-**β** had different effects on human OA mesenchymal stromal cells (OA-MSC) and chondrocytes (OAC). While TGF- **β** stimulated chondrogenesis in OAC, it induced hypertrophy, mineralization, and MMP-13 in OA-MSC (Liu et al., 2020).

SB-505124 is a TGF-**β** type I receptor inhibitor, and it was found in vitro and in animal models of OA that TGF-**β**1 overexpression in osteoclasts was responsible for chondrocyte apoptosis and cartilage degeneration in OA, and SB-505124 could inhibit the degradation of articular cartilage (Zhang et al., 2018).

Tissue Gene-c (TG-C) is a cell-mediated gene therapy that delivers allogeneic chondrocytes expressing TGF-**β**1 directly to the damaged knee joint, consisting of irradiated allogeneic human chondrocytes that express TGF-**β**1 and normal allogeneic human chondrocytes in a 1:3 ratio (GEC-TGF-**β**1) (Ha et al., 2012). Two randomized, double-blind, placebo-controlled phase II studies to evaluate the safety and efficacy of IA injection of GEC-TGF-**β**1 in patients with knee OA (Cherian et al., 2015; Ha et al., 2015). The results showed that most of the adverse events were local reactions and did not require further treatment, and only a small number of patients had allergic reactions but recovered within 24 h. Moreover, compared with the placebo, GEC-TGF-**β**1 could significantly improve pain and physical function. However, neither of these studies evaluated the effect of GEC-TGF-**β**1 on cartilage regeneration and OA imaging changes. The results of a phase III trial (NCT02072070) suggested that GEC-TGF-**β**1 had beneficial effects on pain and functional improvement in patients with OA, but had limited effects on structural improvement (Kim et al., 2018).

Metformin

Metformin is a safe and well-tolerated oral biguanide that has been used as the first-line therapy for type 2 diabetes for more than 50 years. Preclinical studies had shown that Metformin could significantly attenuate articular cartilage degeneration and relieve pain in the OA mouse model (Li H. et al., 2020). Besides, it was found that the chondroprotective effect of metformin was mediated by activation of adenosine monophosphate-activated protein kinase (AMPK) signaling. Metformin could enhance AMPK expression and phosphorylation in chondrocytes, and increase the production of type II collagen and reduce the level of MMP-13 by activating AMPK pathway (Li J. et al., 2020). A nationwide, retrospective, matched-cohort study evaluated 968 patients with OA and type 2 diabetes mellitus (T2DM) during 10 years of follow-up and the results showed that OA patients with T2DM under combination COX-2 inhibitors and Metformin therapy were associated with lower joint replacement surgery rates than COX-

Key points

- **Sprifermin:** A recombinant FGF18 that preserved cartilage thickness and reduced joint space in knee OA, showing limited pain relief (Hochberg et al., 2019).
- **TGF-β1:** Influences cartilage health; the inhibitor SB-505124 showed promise in preventing degradation (Zhang et al., 2018).
- **Tissue Gene-c:** Gene therapy improved pain and function in OA patients, but its impact on cartilage regeneration was not assessed (Kim et al., 2018).
- **Metformin:** Used for type 2 diabetes, it showed chondroprotective effects and lower joint replacement rates in OA patients on combined therapy.

Key points

- **Subchondral Bone as a Target:** Increased bone resorption contributes to OA pathology, making the subchondral bone a potential therapeutic target (Karsdal et al., 2014).
- **Bisphosphonates:** Intravenous Zoledronic Acid showed initial benefits in pain and bone marrow lesions (BMLs), but a recent trial found no significant impact on cartilage loss or pain relief (Cai et al., 2020).
- **Calcitonin:** Two large trials indicated that oral salmon calcitonin did not improve pain or joint space width in symptomatic knee OA (Karsdal et al., 2015).
- **Strontium Ranelate:** Effective in reducing joint space narrowing and pain in OA, but its use is limited by cardiovascular risks (Reginster et al., 2013; Pelletier et al., 2015).
- **Teriparatide:** A recombinant PTH that showed promise in animal studies for reducing cartilage degeneration and promoting matrix regeneration, with ongoing trials to evaluate its efficacy in OA (Macica et al., 2011).

2 inhibitors only (Lu et al., 2018). Recently, a prospective cohort study reported that metformin had a beneficial effect on long-term knee outcomes in obese knee OA patients, and metformin significantly reduced the loss of medial knee cartilage volume (Wang et al., 2019). Currently, randomized controlled trials are still needed to confirm these findings and to determine whether metformin can be considered as a potential disease-modifying drug for knee OA with or without obese phenotype.

Investigational drugs targeting The subchondral bone

Increased subchondral bone resorption and bone turnover contribute to the pathogenesis of OA (Karsdal et al., 2014). Thus, the subchondral bone may be a potential target for OA therapy. However, currently available agents targeting the subchondral bone haven't been approved for the treatment of OA due to the inconsistent efficacy or safety considerations, including Zoledronic Acid, Calcitonin, and Strontium ranelate.

Bisphosphonate

One small randomized clinical trial stated that intravenous Zoledronic Acid was beneficial in improving pain and BMLs in knee OA patients at 6 months (Vaysbrot et al., 2018). BMLs detected by MRI represented areas of high bone turnover and active bone remodeling, and bisphosphonates might be beneficial for patients with high metabolic activity (Kuttapitiya et al., 2017). However, recently, a 24-month multicenter, double-blind placebo-controlled randomized clinical trial assessed the effects of twice-yearly intravenous Zoledronic Acid for 24 months on CVL in patients with symptomatic knee OA and BMLs (Cai et al., 2020). The results showed that Zoledronic Acid did not significantly reduce cartilage volume loss, relieve pain, or improve BMLs. These findings did not support intravenous Zoledronic Acid to treat knee OA. A randomized, double-blind, parallel-group, multicenter, placebo-controlled, dose-ranging study (EudraCT2018-002081-39) to assess the efficacy and safety of IA injection of clodronate for knee OA is currently ongoing, and no results are available.

Calcitonin

A combined reporting of two randomized, double-blind, multicenter, placebo-controlled trials (NCT00486434 and NCT00704847) that included 1176 and 1030 patients, respectively, showed that oral salmon calcitonin (sCT) for 24 months did not improve pain symptoms and joint space width (JSW) measured by X-ray in patients with symptomatic knee OA (Karsdal et al., 2015).

Strontium Ranelate

Strontium Ranelate is indicated for the treatment of postmenopausal osteoporosis (Han et al., 2017). Preclinical studies indicated that it reduced subchondral bone resorption and stimulated cartilage matrix formation in vitro and in rat OA model (Coulombe et al., 2004; Tat et al., 2011; Yu et al., 2013). A 3-year multicenter, randomized, dou-ble-blind, placebo-controlled Phase III clinical trial (SEKOIA trial) showed that Strontium Ranelate significantly inhibited the narrowing of the medial femoral joint space, relieved pain, and improved physical function in patients with moderate to severe knee OA compared with placebo (Reginster et al., 2013). A post hoc analysis of the SEKOIA trial found that Strontium Ranelate was also significantly associated with decreased MRI-assessed CVL and BMLs (Pelletier et al., 2015). However, although Strontium Ranelate has a significant protective effect on the joint structure and clinically relevant improvement of symptoms of knee OA, the use of Strontium Ranelate in OA is limited by its cardiovascular risk, particularly the side effects of thromboembolism.

Teriparatide

Teriparatide is a recombinant human parathyroid hormone (PTH), derived from the 1–34 amino acid fragment of human PTH (Oo and Hunter, 2019). It promotes the proliferation and survival of osteoblasts, which is a bone anabolic therapy for osteoporosis (Sampson et al., 2011). A preclinical study showed that Teriparatide could decelerate cartilage degeneration and induced cartilage matrix regeneration in mice administered a meniscal/ligamentous knee injury (Macica et al., 2011). Teriparatide may become a novel candidate therapy for injury-induced OA. A phase II study (NCT03072147) to assess the chondroregenerative efficacy and safety

of Teriparatide for knee OA is still ongoing, and the estimated study completion date is in 2022.

Vitamin D

A prospective study determined that sunlight exposure and serum 25(OH)D levels were both positively associated with knee cartilage volume in older people, suggesting that vitamin D is an important hormonal contributor to cartilage homeostasis (Ding et al., 2009). Thus, Vitamin D supplementation potentially prevented the progression of OA. However, A 2-year RCT showed that Vitamin D supplementation at a dose sufficient to elevate serum levels of 25-hydroxyvitamin D to >36 ng/ml did not reduce knee pain or CVL in patients with symptomatic knee OA (McAlindon et al., 2013). A multicenter randomized, doubleblind, placebo-controlled clinical trial (VIDEO trial) evaluated the effects of vitamin D supplementation in patients with symptomatic knee OA and low serum 25-hydroxyvitamin D levels (Jin et al., 2016). The results showed that Vitamin D supplementation did not prevent tibial cartilage loss or relieve knee pain over 2 years, but improved physical function (Jin et al., 2016) and reduced joint effusion synovitis (Wang X. et al., 2017). Three post-hoc exploratory analysis were carried out on the VIDEO trial. Vitamin D supplementation and maintaining vitamin D sufficiency (25-hydroxyvitamin D > 50 nmol/L at month 3 and 24) over 24 months might be benefificial for depressive symptoms (Zheng et al., 2019) and foot pain (assessed by manchester foot pain and disability index) (Tu et al., 2020) in patients with knee OA. Maintaining vitamin D sufficiency significantly reduced tibial cartilage volume loss and effusion-synovitis volume, and improved physical function compared with those who did not (Zheng et al., 2017).

Investigational drugs to relieve pain

NSAIDs and opioid drugs are primary pharmacological treatments for pain palliation in OA. But these medications are unsuitable for long-term use because of side effects, and their roles in pain control are limited (McAlindon and Bannuru, 2010; Zhang et al., 2010). Patients with OA continue to suffer from inadequate pain relief. Thus, although the development of drugs that can reverse the structural progression of joint damage in OA is important, it is still necessary to consider the effect of drugs against pain (Karsdal et al., 2016; Miller et al., 2018). Besides, there is also an urgent need to develop new ideal therapies, which are safe, simple, long-acting, and convenient to treat the chronic pain associated with OA.

Monoclonal Antibodies Neutralizing Nerve Growth Factor

NGF is a neurotrophin that stimulates the growth of nociceptive nerve fibers and the expression of nociceptive cell surface receptors (Denk et al., 2017; Vincent, 2020). Almost all structures in the joint are innervated with nociceptive nerve fibers, and elevated NGF levels may be sources of refractory knee pain in OA (Malfait and Schnitzer, 2013; Denk et al., 2017). NGF is therefore an attractive target for novel analgesic agents. Tanezumab, Fulranumab, and Fasinumab are monoclonal antibodies that specifically target NGF and inhibit binding to its receptors (Ghouri and Conaghan, 2019). Tanezumab is the most widely studied and has completed pivotal phase III clinical trials, and Fasinumab is in the midst of phase III clinical trials (NCT02683239, NCT03285646, NCT03161093, and NCT03304379), while Janssen has discontinued the clinical development of Fulranumab, with no active trials being underway (Cao et al., 2020). The US FDA recently has granted fast-track certification (a process designed to facilitate the development and expedite the review of new therapies to treat serious conditions and fill unmet medical needs) for Tanezumab for the treatment of chronic pain in patients with OA or chronic low back pain, and Tanezumab is expected to be approved for clinical use soon.

A meta-analysis of 10 randomized controlled trials enrolled 7,665 patients demonstrated that Tanezumab was superior to placebo in pain relief and improvement in physical function and patient's global assessment (PGA) in knee and hip OA patients (Chen J. et al., 2017). A phase IIb/III clinical trial assessed the efficacy, tolerability, and joint safety of Fasinumab in patients with hip and/or knee OA (Dakin et al., 2019). The results showed that Fasinumab significantly improved pain and function in patients with OA, even in those who obtained little

Key points

- **Vitamin D:** Linked to knee cartilage health, but high-dose supplementation didn't improve pain or cartilage loss in OA.
- **VIDEO Trial:** Vitamin D improved physical function and reduced joint effusion but didn't prevent cartilage loss.
- **Pain Management:** NSAIDs and opioids have limited long-term use; new safe therapies for chronic OA pain are needed.
- **NGF Antibodies:** Tanezumab, targeting nerve growth factor, may soon receive FDA approval after phase III trials.
- **Tanezumab Efficacy:** Tanezumab significantly improved pain and function in OA patients, while Fasinumab also showed pain relief in trials.

Key points

- **Tanezumab:** In phase III trials, Tanezumab improved pain and function in OA patients unresponsive to standard analgesics, particularly at a 5 mg dose.
- **Risks:** Anti-NGF treatments may cause rapidly progressive OA and osteonecrosis, leading to a dose reduction of Tanezumab to 5 mg.
- **Zilretta:** An extended-release formulation of triamcinolone acetonide, Zilretta offers prolonged pain relief and was FDA-approved in 2017 for knee OA pain.

benefit from previous analgesics (Dakin et al., 2019). A phase III clinical trial evaluated 696 patients with hip and/or knee OA who had not responded to or were unable to receive standard analgesics (Schnitzer et al., 2019). Patients received by 2 SC injections of Tanezumab (2.5 mg administered at baseline and week 8 or 2.5 mg administered at baseline and 5 mg at week 8) or placebo at day 1 and week 8. The results showed that Tanezumab was significantly better than the placebo in improving scores assessing pain and physical function, and PGA-OA (Schnitzer et al., 2019). Recently, another phase III clinical trial evaluated 849 patients with hip and/or knee OA who had not responded to or could not tolerate standard-of-care analgesics. Patients received SC Tanezumab 2.5 mg or 5 mg or placebo every 8 weeks (Berenbaum et al., 2020). The results showed that Tanezumab 5 mg statistically significantly improved pain, physical function and PGA, and Tanezumab 2.5 mg significantly improved pain and physical function, but did not improve PGA (Berenbaum et al., 2020).

It should be noted that anti-NGF treatment may lead to treatment-related rapidly progressive OA (PROA) and osteonecrosis (Hochberg, 2015). These serious joint-related adverse events drove the FDA to place a partial clinical hold on NGF antibodies. By reviewing the adverse events reported in clinical trials, it was found a dose-response relationship between osteonecrosis and NGF antibodies, with the dose of Tanezumab ranging from 2.5 to 10 mg and the dose of Fasinumab ranging from 3 to 9 mg (Hochberg, 2015; Lane and Corr, 2017; Dakin et al., 2019). Therefore, the maximum dose of Tanezumab was reduced to 5 mg after resuming the clinical trials in 2015. Importantly, compared with Tanezumab monotherapy, Tanezumab combined with NSAIDs treatment appeared to increase the risk of RPOA (Hochberg et al., 2016). It seemed that more joint replacements had been observed in patients treated with Tanezumab, but most were personal choices and not associated with adverse events (Schnitzer et al., 2019).

The anti-NGF treatment undoubtedly provides great potential for improving the pain and function of patients with severely symptomatic OA, but it carries the risk of aggravating the structural progression of OA (Miller et al., 2017). Therefore, in addition to using the lowest effective dose to mitigate the risk, it is essential to identify the patient population most suitable for this therapeutic approach. Jayabalan and Schnitzer believed that individuals with preexisting joint abnormalities, such as subchondral insufficiency fractures, who were at increased risk for PROA when treated with anti-NGF, should not be considered for the anti-NGF treatment. On the other hand, anti-NGF may be a particularly useful drug for specific populations for whom NSAIDs are contraindicated and/or not recommended (Jayabalan and Schnitzer, 2017).

Intra-articular Corticosteroid

Triamcinolone Acetonide Sustained-Release Agent Triamcinolone acetonide (TA) is an intra-articular corticosteroid to relieve pain, but its magnitude of benefit rapidly wanes post-injection for rapid systemic absorption (Kraus et al., 2018). Zilretta (formerly FX006) is a novel type of extended-release TA formulation in 75:25 poly microsphere, which is designed to prolong TA residence in the joint compared with standard TA crystal suspensions (TAcs) (Conaghan et al., 2018a). A phase III, multicenter, double-blind, randomized controlled trial compared FX006 (32 mg), TAcs (40 mg), and saline placebo in 484 patients with knee OA (Conaghan et al., 2018b). Although FX006 did not significantly reduce the average-daily-pain (ADP)-intensity of OA compared to TAcs at 12 weeks, it reached the primary endpoint of a significant improvement in ADP-intensit compared with placebo. In addition, FX006 significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for pain, stiffness, and physical function, and Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS-QOL) scores for the quality of life at 12 weeks compared with both placebo and TAcs (Conaghan et al., 2018b). FX006 causes less blood glucose elevation compared to standard TAcs in type 2 diabetic patients. For this reason, FX006 has been licensed by the FDA in October 2017 for the treatment of OA-related knee pain.

IA Triamcinolone

A two-year, randomized, placebo-controlled, double-blind trial (NCT01230424) compared Triamcinolone (40 mg), and sa-

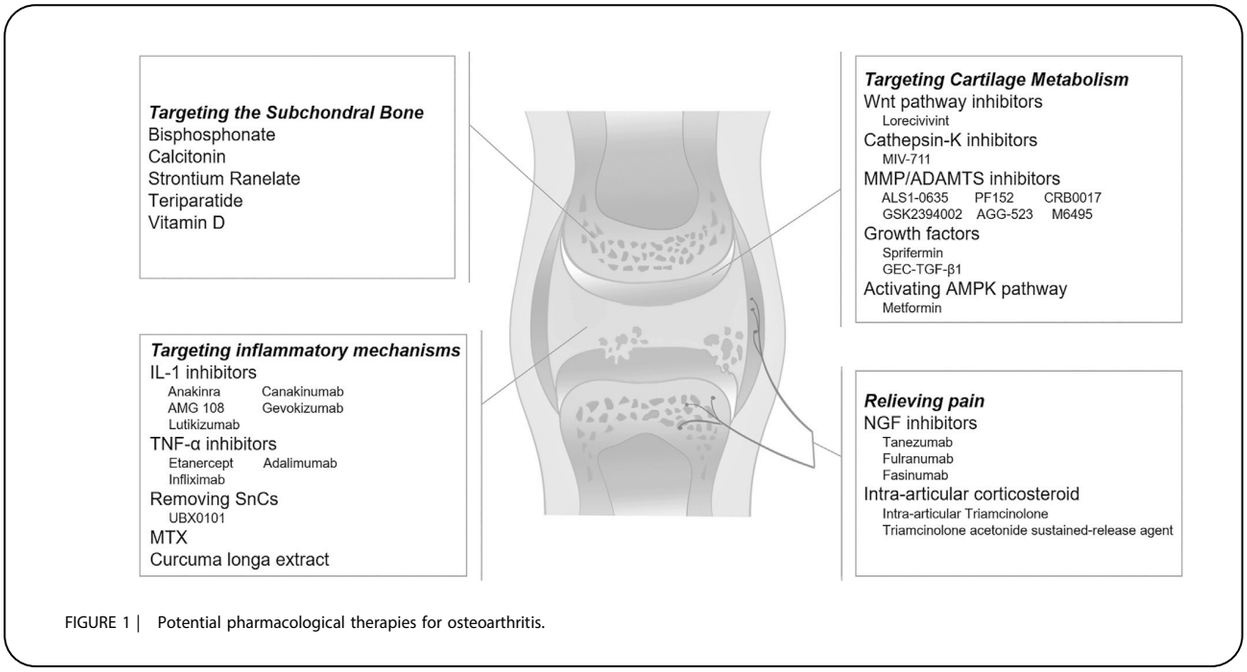

FIGURE 1 | Potential pharmacological therapies for osteoarthritis.

line placebo in 140 patients with symptomatic knee OA. The results showed that IA Triamcinolone every 3 months for 2 years significantly increased CVL and did not improve knee pain (McAlindon et al., 2017). These findings do not support this long-term treatment for patients with symptomatic knee OA.

Expert opinion

OA is a chronic, painful and disabling arthritis with significant burden on the individual and society. With the population aging and obesity, the incidence of OA is increasing as a leading cause of disability worldwide (Peat and Thomas, 2020). To date, no effective drug is able to inhibit the structural damage or reduce long-term disability, or relieve pain with an acceptable benefit-to-risk profile in OA (Latourte et al., 2020). For these reasons, the OARSI led an effort to submit a White Paper to the FDA in support of the designation of OA as a serious disease in 2016. Actually, OA is a severe disease as RA for their similar disability rates, morbidity, costs, and increased mortality rates (Pincus et al., 2019). In the past few years, it has been realized that a complex interaction of multifactorial mechanisms is involved in the pathophysiology of OA. The heterogeneous condition of OA determines that there is no miracle therapeutic strategy fitting for all patients. Also, this heterogeneity may be the major cause for the failure of clinical trials testing therapeutics intended for structure modification or symptom relief in OA.

Various OA phenotypes and endotypes have been explored to overcome this barrier (Deveza et al., 2019), such as synovial inflammatory phenotype, osteoporotic phenotype, articular cartilage degradation phenotype, metabolic phenotype and so on. However, there are few clinical trials to stratify patients based on these phenotype-guided approaches yet. OA phenotyping would be helpful to therapy selection and expedite the development of investigational tailored drugs directly toward variable courses of OA. Metabolomic studies and innovative machine learning approaches may greatly help to determine the key variables to differentiate specific OA subgroups and progression phenotypes (Carlson et al., 2019; Nelson et al., 2019). Nelson et al. observed that baseline variables as BMLs, osteophytes, medial meniscal extrusion, and urine CTX-II were useful to identify progression OA phenotypes at 48 months, while WOMAC pain, lateral meniscal extrusion, and serum N-terminal pro-peptide of collagen IIA (PIIANP) were associated with non-progression phenotypes (Nelson et al., 2019).

Key points

Focus on individualized treatment plans for OA based on patient phenotypes and comorbidities, as current therapies do not adequately prevent structural damage or provide long-term pain relief.

Key points

Establish OA phenotypes to tailor clinical trials and target early to mid-stage patients for more effective DMOAD development.

Establishing OA phenotypes and then setting up distinctive outcome measures for each phenotype is a way to organize more effective and stratified clinical trials in OA in future (Roman-Blas et al., 2020). For example, the synovitis features detected by MRI or ultrasound (US) have the potential to become the useful outcome measures and could be used in clinical trials of new drugs that target synovitis in OA patients with inflammatory phenotype.

To identify the patient population with disease progression is vital to appropriately power clinical trials. The OA patients in the progressed periods are potentially more responsive to interventions, and these patients might be recruited in DMOAD trials to assess the efficacy of a new drug in the future. Sensitive and valid biomarkers are expected to become useful tools to predict OA progression and understand mechanisms of progression (Roman-Blas et al., 2020). On the other hand, OA may only be retarded at early to mid-stages instead of established or advanced OA. To identify the patient population in the early to mid-stages of the disease is also important. Some studies have proposed using MRI or US for the test of disease-modifying approaches and recruiting patients with early diseases as defined on MRI or US in clinical trials (Eckstein and Le Graverand, 2015; Wang et al., 2021).

There is an unmet need for DMOADs. One approach to develop such drugs is to use imaging-assessed joint structural changes such as loss of cartilage volume/thickness, BMLs and synovitis as primary endpoints. However, these endpoints have not been formally accepted by drug administrations. Recently, several authors from The United States Food and Drug Administration proposed a composite endpoint such as "time to total knee replacement (TKR) or severe pain or severely impaired functioning" which can substantially reduce sample size compared to the use of TKR alone (Kim et al., 2020). The endpoints such as this based on direct measures of patients' functions, feels or survive would be more clinically relevant for development of OA drugs. A variety of potential therapeutics targeting on inflammation, cellular senescence, cartilage metabolism, subchondral bone remodeling, and peripheral nociceptive pathway are expected to reshape the landscape of OA treatment over the next few years (Figure 1). The cartilage destruction is the main characteristic sign of OA. Novel agents targeting articular cartilage molecular mechanisms seem to be most promising. Lorecivivint, MIV-711 and Sprifermin are promising agents as DMOADs to slow disease progression. Long-term RCTs are still needed to confirm the safety and efficacy of these novel OA pharmacotherapy medicines.

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Comprehensive Review of Knee Osteoarthritis Pharmacological Treatment and the Latest Professional Societies' Guidelines

Abstract: Osteoarthritis is the most common musculoskeletal progressive disease, with the knee as the most commonly affected joint in the human body. While several new medications are still under research, many symptomatic therapy options, such as analgesics (opioid and non-opioid), nonsteroidanti-inflammatory drugs, symptomatic slow-acting drugs in osteoarthritis, and preparations for topical administration, are being used, with a diverse clinical response and inconsistent conclusions across various professional societies guidelines. The concept of pharmacogenomic-guided therapy, which lies on principles of the right medication for the right patient in the right dose at the right time, can significantly increase the patient's response to symptom relief therapy in knee osteoarthritis. Corticosteroid intra-articular injections and hyaluronic acid injections provoke numerous discussions and disagreements among different guidelines, even though they are currently used in daily clinical practice. Biological options, such as platelet-rich plasma and mesenchymal stem cell injections, have shown good results in the treatment of osteoarthritis symptoms, greatly increasing the patient's quality of life, especially when combined with other therapeutic options. Non-inclusion of the latter therapies in the guidelines, and their inconsistent stance on numerous therapy options, requires larger and well-designed studies to examine the true effects of these therapies and update the existing guidelines.

Keywords: knee osteoarthritis; guidelines; drug therapy; pharmacogenomics; intra-articular injections; mesenchymal stem cells

INTRODUCTION

It is approximated that 250 million people worldwide suffer from osteoarthritis (OA), with an increasing trend in prevalence during the last decades, which continues to rise [1–3]. According to Global Burden of Diseases, Injuries, and Risk Factors Study 2015 by Disease and Injury Incidence and Prevalence Collaborators, approximately 85% of the burden of OA worldwide is connected with knee OA, with an estimated prevalence of 10% in men and 13% in women aged 60 and above [4,5]. OA is challenging to treat. The gold-standard endstage therapy is total joint replacement surgery, without any effective therapeutic option available to stop OA from developing or progressing [1]. As a chronic disease with pain and diminished joint mobility and function as the dominant symptoms, pain management and lifestyle changes are the only available therapeutic option for low-grade OA. Therapeutic measures including intra-articular applications of corticosteroid injections, hyaluronic acid injections, platelet-rich plasma, or mesenchymal stem cells may slow down the existing condition according to some studies. Still, these results are often inconsistent, with different strengths of recommendation across different professional societies' guidelines, as can be seen in Tables 1 and 2 [6–10]. This comprehensive literature review aims to compare recent guidelines for the most-often-used pharmaceutical and biological treatment options and review the recent meta-analyses for potential new insights into these procedures.

2. Literature Search Methodology

To access the most recent literature with the highest level of evidence, a literature search of PubMed was provided using filters for systematic reviews and meta-analyses only, from 1 January 2018 until 10 February 2021. The term knee osteoarthritis was combined with the most commonly used pharmaceutical agents for its treatment using the commands AND and OR. The overall search included the following terms: (knee osteoarthritis) AND ((acetaminophen) OR (paracetamol) OR (opioids) OR (tramadol) OR (morphine) OR (oxycodone) OR (NSAID) OR (ibuprofen) OR (ketoprofen) OR (naproxen) OR (etoricoxib) OR (celecoxib) OR (rofecoxib) OR (DMOAD) OR (SADOA) OR (SYSADOA) OR (glucosamine) OR (chondroitin) OR (topical) OR (corticosteroid) OR (glucocorticoid) OR (methylprednisolone) OR (betamethasone) OR (triamcinolone) OR (dexamethasone) OR (hyaluronic acid) OR (hyaluronan) OR (platelet-rich plasma) OR (PRP) OR (mesenchymal stem cells) OR (MSC) OR (stromal vascular fraction) OR (SVF)). This search generated a total of 133 results, of which after reading the title and/or abstract, 42 papers satisfied the topic and the point of this article. These articles were read in full and included in the review. The 4 guidelines of well-known professional societies for the treatment of knee OA were included to compare the guidelines with the latest and most significant literature. The remaining 61 references were already known to the authors and/or were included in order to increase the quality of the work, improve the readability of the article itself, and write the introduction, the section on pharmacogenomics, and parts of the individual chapters' conclusions.

3. Peroral Treatment

When OA becomes symptomatic, patients start to use some pharmacological agents, either recommended by the doctor or on their own. There is a wide range of agents used in treat-

Table 1. Guideline recommendations for most commonly used oral and topical pharmacological agents in osteoarthritis treatment.

Guideline Author	Year of Issue	Acetaminophen	Opioid Analgesics		Peroral NSAIDs	SYSADOA	Topical NSAIDs
			Tramadol	Other			
AAOS	2013	Unable to give any recommendation	Positive recommendation	Inconclusive	Positive recommendation	Strong recommendation against use	Positive recommendation
ACR/AF	2020	Conditional recommendation for	Conditional recommendation for	Conditional recommendation against	Recommended as first-line treatment	Strong recommendation against use	Strong recommendation for use prior to oral NSAIDs
OARSI	2019	Conditional recommendation against	Strong recommendation against		Recommended as first-line treatment	Not included	Recommended as first-line treatment
ESCEO	2019	Weak recommendation against as single therapy, should be used as rescue medicine in addition to first-line treatment with SYSADOA	Conditional recommendation for as third-line treatment		Recommended as first-line, short-term treatment	Recommended as first-line, long-term treatment for pharmaceutical-grade products	Recommended in addition to SYSADOA and acetaminophen prior to oral NSAIDs

AAOS—American Academy of Orthopedic Surgeons; ACR/AF—American College of Rheumatology/Arthritis Foundation; OARSI—Osteoarthritis Research Society International; ESCEO—European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; NSAIDs—nonsteroidal anti-inflammatory drugs; SYSADOA—systemic slow-acting drugs in osteoarthritis.

Table 2. Guideline recommendations for most commonly used intra-articular options in osteoarthritis treatment.

Guideline Author	Year of Issue	IACS	IAHA	PRP	MSCs
AAOS	2013	Unable to give any recommendation	Not recommended	Unable to give any recommendation	Not included
ACR/AF	2020	Strong recommendation for short-term analgesia	Conditional recommendation against	Strong recommendation against, (heterogeneous studies, lack of preparation and application standardization)	Strong recommendation against (heterogeneous studies, lack of preparation and application standardization)
OARSI	2019	Conditional recommendation for short-term analgesia	Conditional recommendation for a long-term effect where multiple IACS are contraindicated	Strong recommendation against (non-standardized formulations, low-quality evidence)	Strong recommendation against (non-standardized formulations, low-quality evidence)
ESCEO	2019	Weak recommendation for short-term analgesia when patients have a contraindication for the use of NSAIDs or have insufficient analgesia on NSAID therapy	Weak recommendation for, only to be used when patients have a contraindication for the use of NSAIDs or have insufficient analgesia on NSAID therapy	Not included	Not included

AAOS—American Academy of Orthopedic Surgeons; ACR/AF—American College of Rheumatology/Arthritis Foundation; OARSI—Osteoarthritis Research Society International; ESCEO—European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; IACS—intra-articular corticosteroids; IAHA—intra-articular hyaluronic acid; PRP—platelet-rich plasma; MSCs—mesenchymal stem cells; NSAIDs—nonsteroidal anti-inflammatory drugs.

Key points

- **Efficacy Debate:** Acetaminophen is commonly used for OA, but studies show mixed results regarding its effectiveness in relieving pain compared to placebo, particularly for knee OA.
- **Guideline Recommendations:** The ACR/AF recommends acetaminophen for short-term use when other analgesics are contraindicated, while OARSI advises using NSAIDs as first-line treatment for knee OA.
- **Safety Concerns:** Acetaminophen can pose risks, including hepatotoxicity, particularly at high doses, and may be associated with gastrointestinal bleeding and renal issues.
- **Opioid Use:** Opioids are generally not recommended for OA due to their side effects and addiction potential, and are reserved for cases where other treatments are ineffective.

ing symptomatic OA, from acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) to opioid analgesics and cartilage active agents.

3.1. Analgesics

3.1.1. Acetaminophen (Paracetamol)

Acetaminophen is commonly used as a first-line analgesic in the treatment of various painful conditions. Despite its common use, the exact mechanism of acetaminophen action has not yet been established [11]. However, there are increasing doubts regarding the efficacy of acetaminophen in patients with OA [12]. While some researchers recommend acetaminophen as a very potent analgesic, meta-analyses report that acetaminophen in a maximal daily dose does not have a satisfactory effect in knee OA [13]. A recent Cochrane review and meta-analysis including 3541 patients with either hip or knee OA found no statistical difference of subjective pain intensity, physical function, or the observed side effects in the acetaminophen group compared to the placebo [14]. On the other hand, a network meta-analysis by Jung et al. showed that acetaminophen is clinically effective in knee OA patients with mild to moderate pain [15]. The American College of Rheumatology/Arthritis Foundation (ACR/AF) gave a conditional recommendation for acetaminophen use due to its small effect size when used as monotherapy, but it may be used for short-term or periodic use in patients who have a contraindication for other analgesic drugs [7].

It is important to emphasize that clinical improvement is the primary target of analgesic OA therapy; therefore, acetaminophen should not be dropped in these patients altogether but should instead be replaced by NSAIDs as first-line treatment in knee OA and reserved for situations in which they are contraindicated, which is in accordance with the Osteoarthritis Research Society International (OARSI) 2019 guidelines, which gave a conditional recommendation against their use [6]. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) 2019 guidelines gave a conditional recommendation for acetaminophen use only for shortterm rescue analgesia in combination with long-term chondroitin sulfate or glucosamine [9].

The American Academy of Orthopaedic Surgeons (AAOS) was not able to give a recommendation for or against the use of acetaminophen [8]. Acetaminophen should still be prescribed with caution because there are known side effects. In some patients, higher doses or prolonged use of acetaminophen can be hepatotoxic [12]. Comparing the safety profile of acetaminophen with NSAIDs, acetaminophen has fewer adverse effects, but the risk of liver toxicity cannot be neglected. For that reason, the Food and Drug Agency in 2011 issued a warning and communication to drug manufacturers to reduce the dose of acetaminophen in prescription drug products to 325 mg [16].

Concerns in relation to other possible adverse events associated with acetaminophen use have been raised. One observational study found that using high doses of acetaminophen (>3 g/day) is associated with a higher risk of hospitalization due to gastrointestinal bleeding compared to doses of 3 g/day or lesser [17]. Other studies indicated a decreased glomerular filtration rate with prolonged acetaminophen use of daily doses above 3 g and a higher incidence of hypertension [18]. Such concerns have to be acknowledged, but it also needs to be kept in mind that most of the studies reporting these adverse events were observational studies. In addition, acetaminophen was commonly prescribed in the elderly due to their comorbidities and higher susceptibility to NSAID-caused adverse events, thereby creating allocation bias [19].

3.1.2. Opioids

Opioids (tramadol, morphine, oxycodone, etc.) are not readily prescribed in the treatment of OA. Opioid analgesics are agonists of the opioid receptors in the central nervous system (CNS), whose activation leads to CNS depression [20]. They have a well-known side-effect profile, including constipation, nausea, and vomiting, in addition to their very high addiction potential. In a direct comparison to NSAIDs, tramadol was shown to be inferior at short-term (4–12 weeks) physical function improvement and tolerability for neuropathic, low-back, and OA pain [21]. Opioids are generally indicated for short-term OA therapy in patients where other analgesics are unsuccessful or

contraindicated for any reason [22]. They are also a good choice in patients who are not candidates for joint replacement [7,9]. The recommendations of professional guidelines differ on this topic. The AAOS gave a positive recommendation for the use of tramadol in the symptomatic treatment of knee OA; however, it found evidence of the use of other opioids or transdermal patches inconclusive [8]. The ACR/AF gave a conditional recommendation for the use of tramadol, while other opioid analgesics were given a conditional recommendation against use, indicating both should be used only when other therapeutic options have been exhausted[7]. ESCEO guidelines have a similar stance, giving a conditional recommendation for the use of opioids as a third-line therapy option prior to knee replacement surgery when other pharmacological options (including intra-articular corticosteroids and hyaluronic acid (HA)) are unsuccessful in symptomatic relief [9]. The only guideline that gave a negative recommendation was that by OARSI. A strong recommendation against the use of oral or transdermal opioids for OA treatment was given due to their high addiction potential and limited efficacy [6].

According to a Cochrane review, tramadol alone or in combination with acetaminophen had no significant benefit on mean pain or function in patients with OA compared to the placebo [23]. A systematic review and meta-analysis that investigated opioid usage for OA pain found low tolerability of opioids, without clinically relevant efficacy in controlled studies from 4 to 24 weeks for OA pain [24]. Similar findings were reported in a recent meta-analysis by Osani et al. The authors concluded that opioids showed minor benefits on pain and function compared with the placebo from 2 to 12 weeks of treatment, which did not improve the patients' quality of life. Furthermore, the authors indicated that stronger opioids (morphine, oxycodone) displayed inferior clinical results than weak/intermediate opioids (codeine, tramadol) but also increased the risk of experiencing more adverse effects [25]. These latest findings weigh in favor of the negative recommendation given by most guidelines, in our opinion; however, a rational approach on a patient-to-patient basis should be taken to identify the need for opioid therapy where other options have failed, much like the three-step approach recommended by ESCEO.

3.2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs include two groups of drugs: non-selective cyclooxygenase (COX) inhibitorsB and selective cyclooxygenase-2 (COX-2) inhibitors, such as etoricoxib and celecoxib. They have an analgesic and anti-inflammatory effect. Because of their anti-inflammatory effect, they have good efficacy in the treatment of OA-related pain. Nevertheless, these drugs should be used very carefully because of their side-effect profile in chronic use, especially gastrointestinal and cardiovascular effects [26–28]. Gastrointestinal side effects are more likely to occur in patients with some risk factors such as age over 60, high NSAID doses, long therapy duration, co-administration of two or more NSAIDs, and Helicobacter pylori infection [29]. In the cases where this risk is increased, non-selective COX inhibitors in combination with a proton pump inhibitor or selective COX-2 inhibitors should be administered [30]. A study by Nissen et al. investigated the cardiovascular safety of celecoxib, a selective COX-2 inhibitor, and non-selective COX inhibitors (naproxen, ibuprofen). Non-significant differences in the risk of a cardiovascular event were observed between the drugs, but celecoxib showed significantly lower rates of gastrointestinal events than non-selective COX inhibitors and also lower rates of renal side effects compared to ibuprofen [31]. In a systematic review and network meta-analysis of long-term (12 months) trials by Gregori et al., celecoxib was the only NSAID associated with improvements in pain, but the association was small and without observed improvements in physical function [32]. Given only the minor or no clinical benefits of long-term NSAID use and considering the possible risk of adverse effects, NSAID therapy should be restricted only to short-term treatment. Different conclusions have been drawn regarding the most potent NSAID. A meta-analysis by da Costa et al. indicated that oral use of diclofenac 150 mg/day is the most effective for pain management and physical function improvement compared to other NSAIDs such as rofecoxib, lumiracoxib, etoricoxib, celecoxib, ibuprofen, and naproxen [33]. Of all the available NSAIDs, naproxen was found

Key points

- **Opioid Recommendations:** Guidelines differ on opioid use for knee OA. The AAOS supports tramadol, while the ACR/AF recommends it conditionally. OARSI strongly advises against opioids due to addiction risk and limited efficacy.
- **Efficacy Concerns:** Cochrane reviews indicate tramadol and other opioids show minimal benefit over placebo for OA pain, with low tolerability and no significant improvement in quality of life.
- **NSAID Efficacy:** NSAIDs (both non-selective and selective COX-2 inhibitors) are effective for OA-related pain, but should be used cautiously due to potential gastrointestinal and cardiovascular side effects.
- **Short-Term Use Recommended:** Long-term NSAID use offers minor benefits and poses risks; therefore, they should be reserved for short-term treatment to manage pain effectively.

Key points

- **SYSADOA Overview:** Glucosamine and chondroitin sulfate are symptomatic slow-acting drugs for osteoarthritis, but their efficacy is debated.
- **Guideline Discrepancies:** The AAOS strongly advises against their use, while OARSI's recommendations have varied due to weak effects.
- **Potential Benefits:** Meta-analyses suggest glucosamine may reduce pain and improve function, while chondroitin shows better relief compared to placebo.
- **Quality of Supplements:** Efficacy may depend on the preparation quality, with prescription-grade formulations proving more effective than over-the-counter options.

to be the most effective in both symptom relief and positive functional outcomes in a network meta-analysis, which included all randomized control trials in the English language until 2015, that compared the clinical effectiveness of available oral and intra-articular pharmacologic agents (NSAIDs, acetaminophen, corticosteroids, and hyaluronic acid) to each other and to the placebo [34]. The observed results were even stronger when oral naproxen was used with intra-articular corticosteroid application. OARSI, ESCEO, and ACR/AF guidelines agree on the recommendation of oral NSAIDs as first-line short-term therapy for persistent pain in OA patients who are not at high risk for a cardiovascular event [6,7,9,10]. The AAOS gave a positive recommendation for the use of NSAIDs in the symptomatic treatment of knee OA as first-line therapy [8].

The positive results of NSAID therapy are of no surprise from a pathophysiologic point of view, as the key driver of OA progression is a low-grade chronic inflammation caused by an imbalance between anabolic and catabolic processes of the articular osteochondral unit [35].

3.3. Symptomatic Slow-Acting Drugs in Osteoarthritis (SYSADOA)

According to Steinmeyer and co-authors, glucosamine and chondroitin sulfate are in a group of symptomatic slow-acting drugs in osteoarthritis (SYSADOA) [29]. Glucosamine is a metabolic precursor of glycosaminoglycans, which are the components of the cartilage extracellular matrix (ECM), and chondroitin sulfate is a natural component of the ECM [35,36]. Evidence of the positive effects of glucosamine and chondroitin sulfate is still a matter of debate. Official guidelines have different attitudes toward the use of glucosamine and chondroitin sulfate in the treatment of knee OA. The AAOS, in its 2013 guidelines, does not recommend the use of glucosamine and chondroitin for patients with symptomatic knee OA, with a strong strength of recommendation [8]. OARSI gave recommendations for the symptom relief effect and disease-modifying effect for both the drugs separately in its 2014 guidelines but did not include them in its 2019 knee OA guidelines [6,37].

The recommendation for the symptom relief effect was uncertain and for the disease-modifying effect was not appropriate. The main reason for the recommendation was the drug's weak effect and very heterogeneous results between studies [37]. Glucosamine may be used in patients with NSAID intolerance or patients with high gastrointestinal and cardiovascular risk. Although their effect in symptomatic relief of patients with knee OA cannot be denied, ACR/AF guidelines gave a strong recommendation against the use of glucosamine and chondroitin sulfate due to discrepancies in analyzed studies, which indicated a possible publication bias, high placebo effect, and unknown biological mechanisms of their effect [7].

However,recent meta-analyses indicate the potential benefits of therapy with SYSA-DOA in patients with knee OA. A systematic review and network meta-analysis of long-term (12 months) trials found that glucosamine sulfate is related to pain reduction but also improvements in physical function and joint structure [32]. Another meta-analysis concluded that supplementation with glucosamine or chondroitin sulfate reduces pain levels measured by the visual analog scale (VAS) in knee OA patients but do not improve the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score for pain, function, or stiffness[38]. Zhu et al. noticed superior benefits of chondroitin in alleviating pain and improving physical function compared with the placebo and also the role of glucosamine in reducing joint stiffness. They also emphasized a good safety profile and great tolerance of the aforementioned supplements[39]. Different conclusions regarding the efficacy of SYSADOA may be a consequence of various qualities of glucosamine and chondroitin preparations in numerous studies. This idea was corroborated by a recent meta-analysis that marked that prescription-grade chondroitin sulfate and prescription-grade crystalline glucosamine sulfate are more effective in reducing pain in knee OA than nutraceutical grade or over-the-counter (OTC) glucosamine or chondroitin preparations[40]. Similar conclusions were made by Honvo and colleagues, who indicated that prescription-grade preparations with chondroitin sulfate achieve better results for pain and functional status [41]. ESCEO guidelines recommend only pharm-

aceutical-grade chondroitin sulfate and crystalline glucosamine as first-line long-term therapy in symptomatic knee OA as both single therapy and in combination with acetaminophen, distinguishing them from the same products of weak pharmaceutical quality. They do not recommend the use of over-the-counter products containing both chondroitin sulfate and glucosamine [9].

Given the fact that new research does not dismiss SYSADOA as a potential symptomatic therapy for knee OA and that the guidelines do not unequivocally advise against their use, larger placebo-controlled studies with prescription-grade preparations are needed to re-evaluate current guidelines and draw stronger conclusions.

3.4. Pharmacologic Treatment in the Pharmacogenomic Context

New pharmacogenomic research indicates that the often-observed inter-individual differences, based on the patient's genetic make-up, should be taken into consideration when prescribing pharmacologic treatment. This is emphasized with reports of up to 50% of patients using an analgesic treatment who do not experience adequate pain relief and with pain being one of the leading symptoms of OA that can predispose the patients to develop depression if it is not adequately addressed and treated [42,43]. The field of pharmacogenomics aims to identify the genetic markers responsible for variable patient drug responses by looking at the genotype of drug-metabolizing enzymes, transporter proteins, target receptors, and others in order to determine the most effective and safest medication and its dose on a case-to-case basis, in contrast to the currently used one-size-fits- all approach used in clinical practice today. The key information pharmacogenomics brings to the clinician is the net result of different allele combinations, referred to as the enzyme phenotype, which defines its function as reduced, normal, or increased [44].

It should be stated that knowing the genetic profile alone is not enough to completely alleviate pain in patients suffering from musculoskeletal pain. Other factors such as the environment, age, sex, previous medical conditions, and lifestyle greatly contribute to the individual sensation of pain [45]. However, pharmacogenomic research offers a new perspective on some of the most commonly used analgesics to treat OA, such as NSAIDs and opioids.

3.4.1. NSAIDs

The different bioavailability based on the CYP2C8 (a member of the cytochrome P450 family) genotype is shown to play a role in patients developing potentially serious adverse drug reactions with prolonged use of NSAIDs, such as gastrointestinal or cardiovascular events [46]. Single-nucleotide polymorphisms for another member of the cytochrome P450 enzyme family, CYP2C9, have been found to influence the metabolism rate of celecoxib and flurbiprofen. For patients who have a determined poor metabolizer phenotype (CYP2C9 *3/*3), a 50% reduction in the starting dose is suggested to avoid potential side effects; however, it is not part of any official guideline [47]. Another study found an increased risk of gastrointestinal tract bleeding in patients carrying CYP2C8*3 and CYP2C9*2 alleles when using NSAIDs that are the substrate of both of these enzymes, such as ibuprofen and diclofenac [48].

3.4.2. Opioids

Although not commonly prescribed for OA patients, opioid analgesics are a group of drugs most commonly associated with genetic polymorphisms. Tramadol, codeine, and oxycodone are all metabolized by CYP2D6 in the liver and bind to the opioid receptor, both of which have demonstrated the ability to impact the effects and side-effect profile of the drugs [49]. Another enzyme linked to the effect of opioid analgesics is catechol-Omethyltransferase, which degrades endogenous catecholamines. Its polymorphisms affect the analgesic efficacy of an opioid drug [49].

Detailed clinical guidelines are available for the interpretation of pharmacogenomic results based on the CYP2D6 genotype, whilst a focused review of the opioid receptor M1 subunit (OPRM1) and COMT polymorphisms did not produce any therapeutic dosing recommendation due to mixed and insufficient evidence of a clinically relevant effect [50].

Key points

- **Pharmacogenomic Impact:** Individual genetic differences significantly influence analgesic treatment efficacy, with up to 50% of patients not achieving adequate pain relief from medications.
- **Genetic Markers:** Pharmacogenomics identifies genetic markers related to drug-metabolizing enzymes, which can help tailor treatments and dosages beyond the current one-size-fits-all approach.
- **NSAID Metabolism:** Variations in the CYP2C8 and CYP2C9 genotypes affect NSAID metabolism, influencing the risk of adverse effects like gastrointestinal or cardiovascular events.
- **Opioid Polymorphisms:** Opioids, though less commonly prescribed for OA, are affected by genetic variations in enzymes like CYP2D6 and catechol-O-methyltransferase, impacting their efficacy and side effects.

Key points

- **Topical NSAIDs:** Topical NSAIDs (diclofenac, ketoprofen, ibuprofen) have a lower side-effect profile (5-15% serum concentration of oral NSAIDs) and are safer for older patients.
- **Efficacy:** About 60% of patients report a 50% pain reduction after using topical NSAIDs, with gastrointestinal side effects similar to placebo.
- **Guideline Support:** All guidelines recommend topical NSAIDs for knee OA, with the AAOS and OARSI endorsing them as first-line treatments.
- **Intra-Articular Corticosteroids:** These injections provide moderate short-term pain relief but are less effective than physical therapy in the long term.
- **MRI Findings:** Corticosteroid injections reduce synovial tissue volume in knees with inflammation, indicating potential short-term benefits.

The implementation of pharmacogenomic results in daily clinical practice is a challenge because it requires an interdisciplinary team of physicians. However, in the future, with the development of more robust genetic screening platforms and increased numbers of patients willing to test themselves for their unique polymorphisms, new tools should be made available to ease the interpretation of data in a reliable, easy-to-understand, and fast manner, possibly using the advantages of artificial intelligence [51].

4. Topical Treatment

• Topical NSAIDs

Topically used NSAIDs (diclofenac, ketoprofen, and ibuprofen) are a very simple and popular method in the therapy of OA. Their main advantage compared to oral NSAIDs is their side-effect profile, which is greatly reduced, with only 5–15% serum concentration compared to that of oral administration [29]. The most common side effects of topical NSAIDs include skin reactions on the application site, including dermatitis, pruritus, and rash, while systemic gastrointestinal and cardiovascular side effects are rare and less common than after oral use [52]. A Cochrane review showed that gastrointestinal side effects during topical application of NSAIDs are the same as in the placebo group [53]. The effectiveness of topical administration is also very good. According to the same Cochrane review, after topical application of diclofenac or ketoprofen, 60% of patients reported pain reduction by 50% [53]. However, a systematic review by Concoff et al. demonstrated that topical NSAIDs have smaller effect estimates than acetaminophen, intra-articular corticosteroids, and intra-articular hyaluronic acid regardless of molecular weight [54]. Knowing that OA is a condition predominantly affecting the older population, who is at higher risk of experiencing the side effects of prolonged NSAID use due to either underlying medical conditions or polypharmacy potentiating that effect, the reduced side-effect potential is welcomed in this population[55,56]. However, caution should be employed when co-administering oral and topical NSAIDs, particularly in patients who have previously experienced NSAID-related side effects [57]. Guidelines are in unison in their positive recommendation of topical NSAID therapy. The AAOS gave a positive recommendation for the use of topical NSAIDs in the symptomatic treatment of knee OA [8]. OARSI guidelines recommend topical NSAIDs as first-line treatment for pain relief in knee OA, while the ACR/AF gave a strong recommendation for their use and suggested they be used before oral NSAIDs [6,7]. ESCEO guidelines recommend topical NSAIDs to be used before oral NSAIDs when optimal pain relief is not achieved by first-line SYSADOA and acetaminophen [9].

5. Intra-Articular Injections

5.1. Corticosteroid Injections

Corticosteroids are a well-known group of drugs used to treat various inflammatory conditions in almost every field of medicine. Physiologically, they are stress hormones that bind to the glucocorticoid receptor and regulate multiple processes throughout the body by modifying gene expression [58]. Injected corticosteroids treat a targeted location, such as inflammation or pain caused by tendinitis or pain in the osteoarthritic joint.

A Cochrane review of intra-articular corticosteroid injections concluded that corticosteroids could offer moderate pain relief and a little improvement in physical function. Intra-articular corticosteroids were shown to have a similar side-effect profile compared to the placebo. The quality of evidence, however, was considered to be very low for all results, since the analyzed study results were largely inconsistent and the evidence was based on many small studies of poor quality [59].

Even though intra-articular glucocorticoid injections are widely used in clinical practice and have some effect in short-term joint pain improvement, studies are showing its inferiority at 1 year after administration compared to physical therapy [60].

improvement in patients with knee OA, treatment with intra-articular steroids before physical therapy is not associated with additional benefits [61]. A study by O'Neill et al. showed that corticosteroid injection into knee joints with magnetic resonance imaging (MRI)-confirmed synovial thickening significantly reduces synovial tissue volume,

which is correlated with pain reduction [62]. In addition, with the corticosteroid effect wearing off, an increase in both synovial tissue volume and pain recurrence was observed, indicating the potential of repetitive treatment with intra-articular steroids for patients with confirmed synovial inflammation. These results were reinforced by the findings of Mc-Cabe et al., who investigated the relationship between synovial fluid blood cell count and response to therapy with intra-articular steroids, concluding that pain reduction is greater in patients with a higher synovial white blood cell count [63].

However, intermittent injections of corticosteroids were not associated with long-term pain reduction in a systematic review and network meta-analysis of long-term (12 months) trials by Gregori et al. [32]. Still, corticoids were the only intra-articular therapy option (among hyaluronic acid and PRP injections) that had a statistically significant effect on reducing pain compared to the intra-articular placebo according to Jevsevar et al. [34]. The same study ranked intra-articular corticosteroids as the most promising therapy option in reducing pain, with oral NSAIDs and other intra-articular options falling behind. Although intra-articular corticosteroids are widely used as a short-term pain relief therapy option, Saltychev et al. analyzed the magnitude and duration of their effect on pain severity in knee OA. They reported mild to moderate pain reduction for up to 3 months after the initial injection of corticosteroids. Results between corticosteroids differed from a strong effect with betamethasone to statistically insignificant effects with triamcinolone [64]. Nevertheless, a recent network meta-analysis claimed that extended-release corticosteroids (triamcinolone acetonide extended-release injectable suspension) may provide an additional clinical benefit over standard-release corticosteroids (triamcinolone, betamethasone, hydrocortisone, methylprednisolone, and cortisone), but indicated the need for further research comparing the two forms of corticosteroid injections with the placebo [65].

The guidelines again differ in their recommendation of intra-articular corticosteroid therapy. ESCEO gave a weak recommendation for corticosteroids, only to be used when patients have a contraindication for the use of NSAIDs or have insufficient relief on NSAID therapy, for short-term pain relief, suggesting also that a greater effect may be expected in patients with higher pain intensity [9]. OARSI gave a conditional recommendation for the use of intra-articular corticosteroids for short-term pain relief, with a good clinical practice statement indicating an acceptable safety profile for patients with comorbidities [6]. The ACR/AF gave a strong recommendation for the use of intra-articular glucocorticoid injections for short-term pain relief [7]. The AAOS was not able to give a recommendation for or against the use of intra-articular corticosteroids in its 2013 guidelines [8]. Guideline discrepancies should be considered when deciding on intra-articular corticosteroid therapy, bearing in mind its chondrotoxic effect [66,67]. According to the available body of evidence, intra-articular corticosteroids should be reserved for persistent pain in higher-grade OA, as most guidelines agree, perhaps using other intra-articular options for short-term pain treatment in younger individuals and those with low-grade OA.

5.2. Viscosupplementation (Hyaluronic Acid)

Hyaluronic acid (HA) is a molecule from the group of glycosaminoglycans. HA properties vary based on its molecular weight and molecular structure, thus making it a heterogeneous group of compounds rather than a single molecule. The main roles of HA are lubrication of the joint and chondroprotection from mechanical damage [68]. Intraarticular HA injections have an anti-inflammatory, mechanical, and analgesic effect and also a positive effect on proteoglycan and glycosaminoglycan synthesis [69]. Intra-articular HA application is a safe procedure, with only an increased risk of nonserious, transient local reactions reported, as reported in a systematic review and meta-analysis involving more than 8000 patients by Miller and colleagues[70]. In a systematic review by Altman et al., repeated HA injections resulted in the retention or improvement of the positive effects on knee pain, without increased safety risk, stressing the safety of repeated HA injections as one of its advantages [68].

The quality of HA products has been improving in recent years. Thus, high-molec-

Key points

- **Corticosteroid Injections:** Offer short-term pain relief, especially for patients with synovial inflammation. Pain relief lasts up to three months, varying by corticosteroid type.
- **Guideline Recommendations:**
  1. ESCEO: Weak recommendation for short-term use.
  2. OARSI: Conditional recommendation.
  3. ACR/AF: Strong recommendation.
  4. AAOS: No definitive recommendation due to chondrotoxic concerns.
- **Hyaluronic Acid (HA):** Provides joint lubrication and anti-inflammatory effects with a good safety profile for repeated injections.
- **Overall Consideration:** Use corticosteroids for persistent pain in higher-grade OA; consider HA for symptomatic treatment.

Key points

- **Hyaluronic Acid (HA) Efficacy:** High-molecular-weight HA is more effective than non-selective NSAIDs for knee OA, reducing inflammation through receptor interactions.
- **Guideline Recommendations:**
- **OARSI:** Conditional recommendation for HA, effectiveness varies by OA severity.
- **AAOS:** No clear recommendation; some studies favor high-molecular-weight HA.
- **ACR/AF:** Conditional against HA due to limited symptom relief.
- **ESCEO:** Weak recommendation for HA when NSAIDs are insufficient.
- **Patient Selection:** Better outcomes in mild to moderate OA patients, especially those over 60 or with positive initial responses.
- **Platelet-Rich Plasma (PRP):** PRP contains concentrated platelets that release healing factors, but further research on its effectiveness is needed.

ular-weight HA (HMWHA) emerged, which was believed to have a better effect on the joint than low-molecular-weight HA (LM-WHA) [69]. This idea was confirmed by a systematic review that showed a greater effect of hyaluronic acid compared to non-selective NSAIDs and selective COX-2 inhibitors, but only when higher-molecular-weight hyaluronic acid was used for the treatment of knee OA [54]. A systematic review by Altman and colleagues studied the anti-inflammatory properties of intra-articular hyaluronic acid and found that, in contrast to LMWHA, HMWHA possesses not only multivalent sites for CD44 binding but also interacts with toll-like receptor (TLR) and intercellular adhesion molecule-1 (ICAM-1) receptor signaling [71]. Using these mechanisms, HMWHA can downregulate the expression of proinflammatory cytokines, matrix metalloproteinases, prostaglandins, and nitric oxide, molecules responsible for joint inflammation through complex pathophysiologic mechanisms [35]. OARSI and ACR/AF guidelines do not comment on different molecular weights of HA [6,7]. AAOS guidelines state that there are no observed differences for substances over 750 kDa, but HMWHA did show superiority over LMWHA in the studies it analyzed [8]. ESCEO guidelines also commented that the analyzed studies did show the inferiority of LMWHA and that cross-linked HMWHA is associated with a higher occurrence of adverse events [9]. These observations and comments were not included in the final recommendation of these guidelines [8,9].

According to a study by Bowman et al., there are some groups of patients who are more likely to have better outcomes after hyaluronic injection treatment [72]. These are patients with mild to moderate OA, patients older than 60 with moderate OA, and patients who had a positive response to the first injection. According to the same study, patients who respond positively are less likely to undergo knee replacement. Still, Gregori et al. reported no association of hyaluronic acid with long-term pain improvement in patients with knee OA [32].

Although the AAOS could not recommend HA usage for patients with symptomatic knee OA, OARSI gave a conditional recommendation for the use of intra-articular HA for effects over 12 weeks after application, with a good clinical practice statement for patients with comorbidities, while also indicating an acceptable and more favorable safety profile than repeated corticosteroid injections [6,8]. The ACR/AF gave a conditional recommendation against the use of HA in OA, due to a low symptom relief effect when compared to the placebo in studies with a low risk of bias [7]. ESCEO gave a weak recommendation for HA, only to be used when patients have a contraindication for the use of NSAIDs or have insufficient pain relief on NSAID therapy [9].

NSAIDs or have insufficient pain relief on NSAID therapy [9]. A systematic review and meta-analysis by Miller et al. concluded that intra-articular application of hyaluronic acid to the knee joint provides statistically significant, but not clinically important, improvements in pain and knee function, but with a lower risk of side effects compared to orally administered NSAIDs, which are positively recommended by all professional societies' guidelines included in this article [73]. As the guidelines are inconsistent regarding the use of HA in the treatment of knee OA, future research should focus on patient inclusion criteria, particularly to the OA stage and pain levels. Bowman et al. concluded that the application of hyaluronic acid has more effect when therapy is carried out in patients with moderate pain [72]. On the same track were the results of Nicholls and co-workers that demonstrated that intra-articular application of HA, in comparison with the placebo, leads to significant pain reduction in patients with early to moderate OA compared to when the same therapy is administered to patients with end-stage OA [74]. The inclusion of a different patient profile in the studies, with different stages of OA, together with inconsistent HA properties (molecular weight and structure) across studies, can lead to deceptive results and erroneous conclusions regarding the effect of HA therapy.

5.3. Biological Treatment

5.3.1. Platelet-Rich Plasma

Defined as a volume of plasma with a platelet concentration several times higher than in peripheral blood, platelet-rich plasma (PRP) exerts its effect by locally releasing chemokines, cytokines, growth factors, adhesive proteins, proteases, and other small molecules. Based on the leukocyte and fibrin content, there are four general cate-

gories of PRP: leukocyte-rich PRP (L-PRP), leukocyte-reduced PRP (P-PRP), leukocyte platelet-rich fibrin, and pure platelet-rich fibrin [75]. Studies generally agree on the short- and mediumterm analgesic effect of PRP in knee OA; however, it is difficult to draw strict conclusions regarding clinical results due to different modes of PRP preparation and application [76,77]. A recent literature review and meta-analysis including 33 studies on the effect of PRP in OA demonstrated significant positive differences in the VAS, WOMAC, Knee Osteoarthritis Outcome Score (KOOS), and International Knee Documentation Committee (IKDC) scales when compared to HA and the placebo, while the VAS difference was not significant when compared to corticosteroids. In pooled estimates, there was no statistically significant difference noted for adverse events of PRP therapy compared to the control group (placebo, HA, corticosteroids, and mesenchymal stem cells). Multiple injections were also shown to be superior to a single injection, but this effect was only observed when three injections were applied [78]. Similar results regarding the frequency of PRP injections were shown in a meta-analysis by Vilchez-Cavazos and colleagues, where no difference in pain improvement was observed for single versus multiple PRP injections; however, there was a significant difference in functional outcomes at 6 months' follow-up for a triple versus a single injection [79].

These results are further reinforced by a Bayesian network meta-analysis of 30 studies that demonstrated the superiority of PRP to HA, placebo, and corticosteroid injection for VAS and WOMAC scores at 3, 6, and 12 months' follow-up [80]. Two meta-analyses, of 12 and 10 studies, respectively, comparing the effects of PRP and HA, found that patients in the PRP group showed a statistically significant difference in pain reduction (measured by VAS and WOMAC pain scales) at 6 and 12 months' follow-up, while there was no observed difference for clinical outcomes measured by KOOS and other WOMAC scales [76,81]. Meta-analyses, including 20 and 15 studies respectively, comparing PRP to HA by Tang et al. and Han et al. demonstrated a positive effect for both pain and function scores, and a metaanalysis by Zhang et al. reported an improvement in the WOMAC function score at 12 months' follow-up, while there was no significant difference between methods at 6 months after the treatment [82–84]. A meta-analysis by Chen et al. found that WOMAC total scores superiorly improved in patients treated with PRP compared with patients treated with HA [85]. All of the conducted meta-analyses had a common result of statistically significant pain reduction after PRP therapy compared to other intra-articular drugs commonly used, in contrast to functional patient outcomes that have not been consistently reported. This leads to a conclusion that PRP may be the best option for patients who present with pain as the leading symptom for short- to middle-term therapeutic benefit and for patients who present at an earlier stage of OA with mild symptoms [86]. The effect of PRP combined with various other preparations or procedures is an interesting area of research that includes combinations of PRP with stem cells or HA. A recent study observed the effect of treatment with either a single PRP injection or a combination of PRP and hyaluronic acid injection in 78 patients with Kellgren–Lawrence stage 2 OA [87]. It demonstrated that patients achieved better pain relief at 1-month follow-up with a single injection, while the combination group had greater VAS reduction at 6 months' follow-up. There were no other differences between the two groups, indicating that the combined approach could be the method of choice for long-term pain relief in OA patients [87]. A meta-analysis by Zhao et al. demonstrated the greater benefit of combined PRP and HA injection compared to single therapy for both pain scores at 6 months' follow-up and function at 12 months' follow-up [88]. Superior benefits of the combined therapy were corroborated in a systematic review and meta-analysis by Karasavvidis et al., who concluded that patients treated with a combination of PRP and HA had better clinical results for both pain and function (measured by VAS at 3, 6, and 12 months' follow-ups and 12-month WOMAC physical function and stiffness score) compared to patients treated with HA only [89].

The possible therapeutic potential of PRP products in OA is not fully investigated and used, and due to the heterogeneity of study methods with a high risk of bias, the ACR/AF and OARSI guidelines strongly recommend against its use before these problems are resolved in further studies [6,7]. The AAOS was not able to give a recommendation for or against the use of PRP in its guidelines,

Key points

- **PRP Effectiveness:** PRP shows significant improvements in pain (VAS), function (WOMAC), and quality of life (KOOS, IKDC) compared to HA and placebo, but not against corticosteroids. Multiple injections (especially three) yield better outcomes.
- **Meta-Analysis Insights:** Recent analyses confirm PRP's superiority over HA, placebo, and corticosteroids for pain relief at 3, 6, and 12 months. While pain reduction is consistent, functional outcomes are less clear across studies.
- **Combination Therapy:** Studies suggest combining PRP with HA may enhance long-term pain relief and function compared to either treatment alone, with improved outcomes observed at various follow-up points.
- **Guideline Stance:** ACR/AF and OARSI recommend against PRP use due to methodological inconsistencies and bias in studies. AAOS currently offers no recommendation for or against PRP therapy.

Key points

- **MSCs Show Promise:** Mesenchymal stem cells (MSCs) are explored for osteoarthritis (OA) treatment due to regenerative properties.
- **Clinical Use:** BM-MSCs and AD-MSCs provide symptom relief, though mechanisms remain unclear.
- **Guideline Stance:** ACR/AF and OARSI recommend against MSCs due to study inconsistencies; not included in AAOS/ESCEO guidelines.
- **Pain Reduction:** Meta-analyses show significant pain reduction with MSCs, but no major cartilage repair improvements.
- **Research Variability:** Inconsistent MSC sources and methods hinder effective evaluation in clinical outcomes.

and ESCEO did not include PRP in its guidelines [8,9]. A recent systematic review and meta-analysis by Belk et al. was one of many studies demonstrating undeniable clinical improvements of PRP treatment, but it also discussed the leukocyte content in PRP injections. Although having a higher concentration of growth factors, leukocyte-rich PRP has more proinflammatory properties than leukocyte-poor PRP, indicating the need for further research and product standardization [90]. Even though numerous studies with a high level of evidence show excellent clinical improvements in patients with knee OA treated with intra-articular PRP injections, product characterization and dosage, as well as proper timing, treatment repetition period, and application technique, need to be standardized for guidelines to consider including PRP in OA treatment protocols.

5.3.2. Mesenchymal Stem Cells (MSCs)

Articular cartilage, the main affected tissue in OA, has a limited capacity for self-renewal. Since OA is a complex pathophysiological entity involving the whole joint, research efforts have been made to identify key regulating factors that could be used in the pharmacologic treatment of OA [35]. Because of their in vitro ability to differentiate into a variety of cell types and their regenerative and immunoregulatory properties, MSCs have attracted great interest in OA treatment. The persistence of mesenchymal stem cells was first demonstrated in the bone marrow, after which their existence was also confirmed in other tissues such as fat, peripheral blood, placental tissue, umbilical cord, synovial tissue, and dental pulp [91]. Autologous bone-marrow-derived MSCs (BM-MSCs) and adipose-derived MSCs (AD-MSCs), also frequently called adipose-derived stromal vascular fraction (AD-SVF), are currently predominantly used for the treatment of knee OA (previously cultured or directly isolated and applied), while other cell sources such as synovial or allogeneic placental tissue require more testing to enter everyday clinical practice [92,93].

In the natural course of OA, intra-articularly applied MSCs accumulate in joints and adjacent bone marrow lesions, suggesting their role in the response to joint injury, but the mechanism by which stem cell therapy may be effective in OA remains unclear [94,95]. Nevertheless, MSCs are increasingly used in clinical practice, with reports of their benefits regarding symptom relief and joint functionality [96–98]. However, a strong recommendation against the use of MSCs has been made in the ACR/AF and OARSI guidelines due to the various methodology (discrepancies in tissue origins of MSCs, cell numbers, and culture methods) and application strategies used in clinical studies that may influence therapeutic effects and, therefore, the clinical response [6,7]. MSC therapy was not included in AAOS and ESCEO guidelines [8,9].

Despite the negative recommendation by the key opinion makers, a number of clinical and scientific efforts have been made in the research on MSCs in OA treatment in the past 10 years. A meta-analysis that included five randomized controlled trials (four with BMMSCs and one with AD-SVF) with 220 patients found a statistically significant reduction in pain intensity analyzed by the VAS and the Lysholm scale, but no difference in WOMAC. Functional outcomes analyzed by Lysholm and WOMAC scores demonstrated a significant improvement with a standard mean difference of 0.53%. This analysis also indicated that there were no differences in cartilage repair on an MRI examination [99]. Another meta-analysis looked at randomized controlled trials (RCTs) examining culture-expanded MSCs in OA treatment. It included a total of six studies (four with BM-MSCs, one with ADMSCs, and one with placenta-derived MSCs) and 203 patients and reported a statistically significant reduction in pain symptoms measured by both the VAS and WOMAC. However, it also did not find any significant difference in cartilage repair based on MRI analysis or the whole-organ magnetic resonance score (WORMS) [100]. Another meta-analysis by Ma et al. looked at 10 RCTs (4 with BM-MSCs, 3 with AD-MSCs, 1 with adipose-derived mesenchymal progenitor cells (AD-MPCs), 1 with umbilical cord MSCs, and 1 with placenta-derived MSCs), excluding studies where there was a surgical intervention additional to MSC application. Their results demonstrated a significant reduction in perceived pain by the VAS and WOMAC and better stiffness, functionality, and total WOMAC scores for patients randomized to MSC treatment compared to the controls. They also reported increased cartilage volume in the MSC group; however, there was no significant difference in WORMS [101].

These observations were further reinforced in another meta-analysis including 19 studies (15 RCTs, 2 retrospective studies, and 2 cohort studies, of which 9 studies were with AD-MSCs, 5 with BM-MSCs, peripheral blood stem cells in 1 study, and MSCs from a fetus in 4 studies) that found statistically significant pain relief effectiveness measured by the VAS at 12 months' and KOOS and WOMAC at 6 months' follow-up. The included studies demonstrated no side-effects of intra-articular MSC therapy [102]. In a systematic review and meta-analysis by Maheshwer and colleagues including 25 studies, a different result was observed, as demonstrated by no significant pain improvement, but a functional and cartilage volume improvement (0.66 and 0.84 standardized mean difference (SMD), respectively) [103]. They did, however, note that the observed cartilage quality did not reach statistical significance in the analyzed studies. The studies analyzed included different origins of mesenchymal stem cells, such as synovial tissue (1 study), bone marrow aspirate (8 studies), adipose tissue (14 studies), peripheral blood (1 study), and human umbilical cord blood (1 study). The potential of bias in the analyzed studies was high with 17 of 25 analyzed studies being graded as poor or fair [103]. A broader systematic review including 17 studies (6 RCTs) using adipose (6 studies with AD-SVF, 2 with AD-MSCs), bone marrow (8 studies), and umbilical-cord-blood- derived MSCs (1 study) offered the same conclusions in terms of patient-reported pain and functionality outcome, with 15 of 17 included studies reporting this outcome. Regarding cartilage repair, the results differed as 9 of 11 stud-ies reported improved cartilage state on MRI and 6 of 7 on a second-look arthroscopy [104]. A systematic review by di Matteo and colleagues including 23 studies (10 studies used a bone marrow aspirate concentrate and 13 studies used AD-SVF) assessed the studies by analyzing minimally manipulated mesenchymal stem cells and found a significant short-term benefit observed as an improvement in both pain and functional scores analyzed [105]. Follow-up times of included studies ranged from 6 to 34 months for stromal vascular fraction (SVF) studies and 24 days to 24 months for the bone marrow aspirate concentrate (BMAC). An included study had a follow-up of 8 to 16 years, but its design was different from the other included studies as it observed patients with osteonecrosis secondary to corticosteroid use. They also found no significant side effects associated with MSC application. The methodology of the analyzed studies was flawed as it included various adjuvant therapies to SVF, such as PRP or HA, and also different methods of administration, therefore skewing the exact effect of SVF on the analyzed outcomes and cartilage repair. Even though it did not offer any recommendations as it demonstrated a lack of high-quality studies or a straight clinical protocol being used, their study pointed out the short-term benefits of MSC therapy [105]. These studies reinforce the current evidence of the short-term benefits of MSC therapy for knee OA, with a side-effect profile that allows regular clinical intervention. We believe it is important to emphasize that the conducted meta-analyses and systematic reviews did report a high risk of bias in the examined studies and inconsistencies in study protocols. Problems associated with MSC therapy include dosing, harvest site, the number of delivered MSCs, and the characterization of delivered cell populations, as there is no standard procedure that can answer these questions. Proper product characterization is a step in the right direction for these procedures and should be performed to compare the MSC application techniques delivered [106]. Therefore, we believe the future of MSC research and therapy is to provide a method that is available to address these concerns and demonstrate clinical effectiveness in a large multicentric RCT.

6. Conclusions

Non-operative OA treatment is an ever-growing research field with a common goal of finding both the best symptomatic treatment and a disease-modifying treatment that would slow down or altogether stop further development of OA. In clinical practice, patients who present with OA are most commonly of older age, at which other comorbidities are a factor that has to be included in the individual treatment algorithm, therefore making it increasingly difficult to form universally applying treatment guidelines [107]. The guideline development process includes thorough literature reviews and a general consensus among physicians; therefore, discrepancies among guidelines are always expected. However, we believe that a more frequent guideline revision protocol should be implemented as the research pace in the field is great. In addition, the guidelines do not differentiate between the treatment of early and late OA. Updating the

Key points

- **Effectiveness:** MSC therapy shows significant pain relief and functional improvements in OA, particularly with adipose-derived and bone marrow-derived MSCs.
- **Contradictory Findings:** Some reviews report no significant pain improvement, though functional gains and cartilage volume increases are noted.
- **Cartilage Repair:** Mixed results exist regarding cartilage repair; some studies show improvement on imaging and arthroscopy.
- **Safety Profile:** MSC therapy generally has a favorable safety profile with no major side effects reported.
- **Research Gaps:** High bias risk and methodological inconsistencies highlight the need for standardized protocols and multicentric RCTs to confirm clinical effectiveness.

Key points

Revised osteoarthritis guidelines and focused research on PRP and MSC treatments could improve early-stage patient outcomes and reduce disability.

guidelines in this sense could have a positive effect in terms of slowing the course of the disease in many patients who have been diagnosed with OA at an early stage, thus significantly reducing the degree of disability as a consequence of late-stage OA. Furthermore, the research design should focus on providing answers to questions posed in the guideline development process, such as the heterogeneity of PRP and MSC procedures. New information gathered using this method would provide better-quality evidence necessary to establish better treatment protocols for knee OA.

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Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature

Abstract: Patient-reported outcomes (PROs) reflect the patient's perspective and are used in rheumatoid arthritis (RA) routine clinical practice. Patient global assessment (PGA) is one of the most widely used PROs in RA practice and research and is included in several composite scores such as the 28-joint Disease Activity Score (DAS28). PGA is often assessed by a single question with a 0–10 or 0–100 response. The content can vary and relates either to global health (e.g., how is your health overall) or to disease activity (e.g., how active is your arthritis). The wordings used as anchors, i.e., for the score of 0, 10, or 100 according to the scale used, and the timing (i.e., this day or this week) also vary. The different possible ways of measuring PGA translate into variations in its interpretation and reporting and may impact on measures of disease activity and consequently achievement of treat-to-target goals. Furthermore, although PGA is associated with objective measures of disease activity, it is also associated with other aspects of health, such as psychological distress or comorbidities, which leads to situations of discordance between objective RA assessments and PGA. Focusing on the role of PGA, its use and interpretation in RA, this review explores its validity and correlations with other disease measures and its overall value for research and routine clinical practice.

Keywords: Rheumatoid arthritis, Patient global assessment, Discordance

BACKGROUND

Patient-reported outcomes (PROs) are increasingly recognized for their value in providing the patient's perspective on aspects of their condition or their overall health status. Their incorporation into clinical practice and in research in rheumatoid arthritis (RA) is widely supported by international organizations and professional bodies [1, 2], including the European Patients' Academy on Therapeutic Innovations (EUPATI; http://www.patientsacademy.eu/index.php/en/) and the Patient-Centered Outcomes Research Institute (PCORI; http://www.pcori.org/research-results) in the United States, as well as regulatory agencies such as the Food and Drug Administration (http://www.fda.gov/) and the European Medicines Agency (http://www.ema.europa.eu/ema/), all of whom recognize the patient's unique position in providing direct feedback on their disease.

Patient global assessment (PGA) is one of the most widely reported PROs in RA. The considerable burden of RA on the individual is related to both inflammation and damage but also to broader aspects of disease, including psychological and societal impact. The use of PROs like the widely used Health Assessment Questionnaire (HAQ) or the PGA allows a more holistic assessment of disease beyond objective measures of inflammation or structural damage, such as acute phase reactants or radiographic damage. Experts from the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the Outcome Measures in Rheumatology Clinical Trials (OMERACT) have endorsed a "core set" of data for use in RA clinical trials which includes PGA [3, 4]. In recent randomized controlled trials and observational studies in RA, PGA has been reported in 49 % of studies, making it the second most frequently collected PRO after physical function (68 %) [5]. PGA is also incorporated into several of the major outcome and disease activity scores in RA, often as the only PRO: these include the ACR/EULAR remission criteria, the 28-joint count Disease Activity Score (DAS28), the Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI), and the Routine Assessment of Patient Index Data (RAPID3).

However, the use of PGA in RA presents many challenges and limitations. The several possible ways of measuring PGA, including the intended assessment or underlying concept (i.e., global health versus disease activity) and variations in wording/phrasing and time period assessed may lead to differences in interpretation of PGA. Discordance with objective RA measures is also an issue that needs to be addressed. The latter is particularly important in the context of treating to target aiming for remission and shared decision-making [6, 7]. What the different formulations of PGA are, their impact, and justifications for their use remain to be clarified.

To provide readers with a complete overview regarding PGA in RA, a review of the literature was undertaken based on a hierarchical literature search including hand searches and expert opinion searches covering key publications in the field. The objectives were to explore the value of PGA as an outcome measure in RA, focusing on its psychometric properties (feasibility, validity, reliability, and sensitivity to change). Specifically, this review discusses the validity and impact of different wordings/ phrasings and time period assessed as part of PGA on patients' assessment of disease, as well as discordance between physician global assessment and PGA.

Key points

- **Dual Assessment:** PGA captures both overall health and disease activity in rheumatoid arthritis, potentially leading to interpretation discrepancies.
- **Wording Influence:** Variations in PGA phrasing can significantly affect patient responses, necessitating standardization for consistency.
- **Reference Period Impact:** Differences in reference periods for PGA may compromise outcome reliability, emphasizing the need for clear time frame definitions.

Description and practical application
Concepts behind PGA

PGA was developed in the late 1970s and was initially designed for the measurement of self-assessed pain in RA [8], although it has since been used to evaluate RA more globally. It is interesting to note that the way PGA is used in clinical practice covers, in fact, two very different concepts, one related to global health and the other to overall disease activity. They are both usually used under the heading of PGA without further specification for which is being assessed.

PGA wording and phrasing

It is well-recognized that the wording/specific phrasing used for PROs may result in a varied response [9–12]. In the case of PGA, its exact wording/phrasing was not specified when developed; however, it was suggested that it could be used for two main purposes—either a patient assessment of global health or of disease activity—stemming from the two basic concepts (Table 1) [11, 13]. Over the past years many different wordings/phrasings of PGA have been formulated, covering variations of these two concepts [14–18]. Furthermore, anchor wordings may also vary, e.g., words used to describe the right end of the score (corresponding to scores of 10 or 100) from "worst possible" to "most active" to "very active", for example.

Although the wording/phrasing of PGA remains unstandardized to date, the ACR/EULAR remission criteria do specifically propose the following phrasing related to disease activity: "Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?" [19].

PGA reference period

Aside from different wording/phrasing used for the question stem, the reference periods to describe the time component (i.e., the period of recall the patient should refer to when answering the question) can also vary (Table 1). As we will see in this review, the different formulations of PGA lead to differ-ences in interpretation.

In the context of a EULAR taskforce to standardize data collection across registries, in 2015 we contacted registries and cohorts across Europe to explore outcomes being assessed: 52 out of 67 (78 %) registries were collecting some form of PGA [20]. The versions of the PGA used varied with regard to the concept, wording/phrasing, and reference period used. More recently, a smaller pilot survey in 2016 (unpublished data) indicat-

Table 1 Different concepts covered by PGA and examples of different types of wording used

Concept	Attribution to RA	Example question	Reference period
Disease activity	Related to arthritis	"Considering all the ways your arthritis has affected you, how active do you feel your arthritis is."	Today Over the past 2 days Last week Last month Unspecified time period
		"Considering the tenderness, pain, and swelling ofjoints, how active is your rheumatoid arthritis ..."	
		"In general, how active has your rheumatic condition been?"	
		"How active do you consider your arthritis?"	
		"In terms ofjoint tenderness (i.e., joint pain associated with light touch) and joint swelling (i.e., joint enlargement due to inflammation), how active would you say your rheumatic condition is today?	
	Overall	"How do you estimate your disease activity"..?	
Global health	Related to arthritis	"Considering all the ways your arthritis has affected you, how would you say your health is"	
		"Considering all the ways in which your illness affects you at this time, please make a mark below to show how you are doing"	
		"How has your arthritis affected you today?"	
		"Considering all the ways your arthritis affects you, rate how well you are doing on the following scale.."	
	Overall	"Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing"	
		"In general how would you say your health is"	

ed that 6/16 (38 %) cohorts were assessing disease activity-PGA (either related to RA or not specifically related to RA) whereas 6/16 (38 %) were assessing global health PGA and 4/16 (25 %) were assessing both concepts. Some wordings as translated by the investigators are shown in Table 1. With regard to the reference period, 41 % reported "today" as being the time reference used, with the second most common being "last week" (35 %).

PGA scoring

Depending on the type of score used, the PGA can range from 0–100 mm, although is often reported from 0– 10 cm. Higher scores represent a higher level of disease activity or a worse global health. The proposed definition of "low global assessment" is ≤2.0 (scale 0–10) [21].

PGA may be scored using a numeric rating scale (NRS), a verbally administered NRS, or a visual analogue scale (VAS). The PGA-VAS is classically anchored on an unnumbered 10-cm/100-mm horizontal line but may also be administered as a vertical VAS. The VAS may be anchored at the ends (e.g., with defined adjectives at the ends such as best versus worst) or open. Sometimes the PGA is presented with tick marks at periodic intervals or as a VAS consisting of 21 circles at 0.5-mm intervals, the latter shown to be similar to a classic 10/100 scale [22]. In practice, sometimes these exact definitions are not followed (e.g., the line is not 10 cm long or there are not 21 circles evenly spaced) and these technical difficulties may hamper the use of PGA (as is the case with other PROs). A Likert-style scale may also be used, though its metric properties are different.

A study comparing responses to a global health VAS presented both as a 10/100 cm horizontal scale with no incremental markers and as a vertical 20/100 cm VAS with 1-cm markers concluded that different presentation of scales, order effect, and incremental markers can affect scoring [14]. Another study comparing different scaling of PGA revealed similar construct validity for VAS and NRS but higher sensitivity to change of VAS [23]. Although some differences can be seen in scoring methods for PGA, all methods appear at this point similarly valid. We would, however, recommend the use of either an unnumbered horizontal VAS or a numbered horizontal NRS since these formats are the most usual and most used.

Psychometric properties of PGA

The main strengths and weaknesses of PGA are summarized in Table 2. Below, we review each psychometric property of PGA.

Feasibility

Like other PROs, including, for example, the HAQ, PGA is a very feasible measure. PGA is administered as a simple, single-item (with no subscale), patient-completed question measuring the overall way RA affects the patient and/or disease activity at a specific point in time. There is no cost attached to it, it is practical, and can be self-administered. The single question takes only a few seconds to ask, making it feasible in routine clinical settings but also as an end-point in clinical trials in RA and is one of the main strengths of the PGA, making it one of the most frequently reported domains across published RA studies [6].

Face validity

PGA is a global, "gestalt" measure of disease which appears to encompass many aspects of disease which are important for patients. Physicians' assessment of RA disease activity is mainly driven by objective criteria, i.e., tender/ swollen joint counts and level of inflammation, whereas it seems patients place more focus on overall well-being, levels of pain, and health-related quality of life [24]. The latter, in particular, seems to have the greatest relevance and meaning to patients. However, it is often difficult to capture health-related quality of life with simple questionnaires. In this sense, PGA appears of interest since it may summarize in one simple measure many aspects of disease and health which are important to patients.

Although PGA has high face validity (Table 2), it does present some challenges. A major point is the patient's interpretation of the PGA, both depending on the concept (i.e., global health versus disease activity) and on the patient's individual comprehension of this broad question. For both concepts behind PGA, a criticism is that the response to the question may both reflect a broad understanding of the patient's health and also be influenced by a number of factors, making it difficult to discern what aspect of disease contributes to the overall score. Structural

Key points

- **Scoring Range:** PGA typically ranges from 0–100 mm or 0–10 cm, with higher scores reflecting worse disease activity or global health, and a score ≤2.0 indicating low global assessment.
- **Assessment Methods:** Various methods, including numeric rating scales (NRS) and visual analogue scales (VAS), are used for PGA scoring; consistency in the format is essential for accurate results.
- **Feasibility:** As a simple, single-item measure, PGA is quick to administer, making it practical for routine clinical use and clinical trials, with no associated costs.
- **Face Validity:** PGA captures multiple aspects of a patient's health, particularly pain and overall well-being, but its interpretation can vary among patients, affecting the reliability of the score.

Key points

- **Interpretation and Reliability:** PGA interpretation can vary based on disease duration and patient expectations, leading to potential "response shifts." While PGA shows generally high test-retest reliability, studies indicate that it is sensitive to change, making it effective for tracking treatment responses in RA, even better than tender joint counts in some cases.

damage (related to disease duration) and other aspects of patients' lives (such as comorbidities or psychological distress) may have an impact on the scoring of PGA [1].

In both cases of PGA (i.e., global health versus disease activity), interpretation of the question by the patient may depend on duration of disease through a "response shift" (i.e., a change in the meaning of a patient's self-evaluation) resulting from a better knowledge of symptoms and changes in patient expectations [25]. In the current biologic era, however, cumulative damage is considerably lower despite longer disease duration and therefore the effect and meaning of a response shift may have a different interpretation. Differences in patients' perceptions regarding internal standards, values, or conceptualization of health-related quality of life can result in "ambiguous" or "paradoxical" findings [25]. For example, patients with long-standing disability may report a good or high quality of life (despite what externally might appear paradoxically untrue) due to several factors, such as acceptance and the opportunity to adjust and achieve stability through several transition phases while living with disability. All these factors need to be taken into account when interpreting individuals' PGA scores.

Reliability

Data on the reliability of PGA, which refers to the reproducibility in a test–retest setting, are reassuring [26–28]. Studies have shown the PGA intraclass correlation coefficient (as a measure of test–retest reliability) to be generally acceptable to high, though lower than ones noted for physician global assessment [29, 30]. The data available in the literature do not allow us to directly compare reliability of PGA–global health versus PGA–disease activity; although when tested separately, both appear to have acceptable reliability.

Sensitivity to change

Sensitivity to change indicates that the measure will improve when the underlying conceptual framework (here, either global health or disease activity) improves. PGA has been shown to be sensitive to change, which makes it a very useful clinical measure in assessing RA, particularly in clinical trials. PGA detects improvement after active treatment better than, for example, tender joint count [31]. Table 3 summarizes key findings in this area. Furthermore, PGA has been shown to discriminate active treatment from placebo in randomized controlled trials, with treatment-associated changes being congruent with measures of inflammation, suggesting close reflection of other criteria related to the RA process, such as joint counts [32].

Table 2 Major strengths and weaknesses of PGA in RA

Strengths	Weaknesses
Practical and feasible to collect: much more easily collected than joint counts, acute phase reactants, or radiographic damage (simple, single-item tool)	Heterogeneity in concept (i.e., global health versus disease activity) and attribution to RA or other co-existing health conditions and wording/phrasing, all leading to possible heterogeneity in the responses
No cost, non-invasive and self-administered	Heterogeneous phrasing of the time-frame (today, last week, etc.) applied to PGA
May summarize all aspects of disease important to the patient (face validity)	Very broad concept leading to interpretation difficulties
Practical and feasible to interpret: easy to score, incorporate in composite scores, and analyze	Difficulties ofinterpretation due to uncertainty regarding attribution to permanent damage related to RA compared to inflammation and disease activity
Good test–retest reliability	Difficulties ofinterpretation due to uncertainty regarding attribution to RA versus non-RA disease, including psychological distress and comorbidities
Good sensitivity to change in clinical trials	May be influenced by patient education level
Discordance between PGA and physician assessment: brings in additional information	Discordance between PGA and physician assessment: what impact on decision making?

In support of the above, in an analysis of the efficiencies to distinguish active treatment from control treatments in clinical trials, among the seven RA core set measures, the highest relative efficiencies were for the physician global estimate followed by PGA and physical function [33]. "Objective" measures of disease, such as acute phase reactants and tender and swollen joint counts, were not superior to "subjective" global estimates of the physician or patient self-report measures of physical function or pain to differentiate active from control treatments. These findings challenge the view that laboratory and clinical examination findings are more robust than patient self-report measures in assessing and monitoring disease progression and treatment response in RA [33].

Consequences of different wordings/ phrasings

The heterogeneity in the wording/phrasing of PGA requires caution when interpreting the results [34]. The DAS28 is one of the most commonly used composite scores in routine clinical practice; the PGA component of the score carries a small weighting of 0.014, which may still result in differences to the overall DAS28 score (the maximum difference being 1.4 when holding the other variables constant and using first a PGA-VAS score of 0 mm, then of 100 mm). French et al. [11] performed a study where DAS28 was calculated in the same patients when using different PGAs. Five different versions of the PGA-VAS were assessed based on: (1) "Feeling" ("How do you feel concerning your arthritis over the last week?"); (2) Disease activity ("How active has your disease been this week?"); (3) "Well-being" ("How has your overall well-being been this week?"); (4) "Best/worst" ("If 0 is the best you have ever been and 100 is the worst you have ever been, where do you think you have been over the last week?"); and (5) "Arthritis impact measurement scales" (AIMS; "Considering all the ways your arthritis affects you…."). All PGA-VAS versions correlated strongly with each other (rho = 0.67– 0.87, $p < 0.0001$) [11]. However, when the phrasing of PGA varied there was a difference in DAS28 scores, the largest being 0.63 points. Such differences in score, though small, could have clinical implications, i.e., on the eligibility for biologic disease-modifying antirheumatic drugs in countries where access to these drugs is restricted based on strict DAS28 cutoffs.

However, although there are differences at

Key points

- **Wording Variations Affect Scores:** Differences in PGA wording can lead to DAS28 score variations of up to 0.63 points. This may impact clinical decisions, such as eligibility for biologic drugs, highlighting the need for standardized phrasing in assessments..

Table 3 Sensitivity of PGA to change in disease activity and comparison with other measures of disease

Study group	Study details	Main findings
Kaneko et al. 2014 [46]	Prospective study Newly diagnosed RA 75 patients Discordance between PGA and EGA	PGA more sensitive for indicating progressive joint destruction and functional impairment when compared with EGA Discrepancy directed toward a worse assessment by patients
Pope et al. 2009 [52]	Prospective study of a large clinical practice 225 RA patients MID estimates for: (1) HAQ-DI improvement and worsening using PGA anchor; and (2) pain using a patient-reported pain anchor.	MID scores for HAQ-DI in clinical practice were smaller than those seen in clinical trials MID scores were influenced by baseline HRQOL scores and may be influenced by disease duration MID changes were different for worsening (usually needing a larger value) than for improving MID for deterioration was much less than for improvement in patients with more pain and impairment in physical function
Wells et al. 2008 [31]	Randomized controlled trial comparing abatacept (n = 258) with placebo (n = 133) in anti-TNF poor respondents (ATTAIN study) Evaluation of the responsiveness of PROs in RA patients	PGA had larger relative percentage improvement with treatment (24 %) than the generic quality oflife outcomes SF-36 domains and component scores (range 8–21 %) PGA was more efficient than TJC in detecting a treatment effect PGA was found to be in close proximity to the ESR, physician global assessment and the PROs pain assessment, HAQ, bodily pain and physical component score in terms of the standardized response means
Lassere et al. 2001 [53]	Literature review on reliability for different classes of RA measures	The SDD for the PGA (as well as for SJC, TJC, and pain) was found to be large and it had poor reliability compared to multi-item measures of physical and psychological function and radiologic measures
Ward 1994 [54]	Prospective study 24 RA patients Determination of the relative accuracy and sensitivity to change of 14 measures commonly used to assess arthritis activity	High correlation between EGA, PGA, and pain scores The PGA along with other measures of disease severity have been shown to be more sensitive to change than laboratory measures (ESR)

EGA estimator global assessment, ESR erythrocyte sedimentation rate, HAQ-DI Health Assessment Questionnaire-Disability Index, HRQOL Health Related Quality of Life, MID minimally important difference, PGA patient global assessment, SDD smallest detectable difference, SF-36 36-item Short Form Health Survey, SJC swollen joint count, TJC tender joint count, TNF tumor necrosis factor

Key points

- **PGA's Role in Remission:** PGA is essential for determining remission in RA, with ACR/EULAR criteria requiring a score of ≤1.
- **Limiting Factor:** High PGA scores can prevent remission, even without visible inflammation, necessitating a reassessment of remission definitions.
- **Near-Remission States:** Many patients are in "near-remission," meeting most criteria but not PGA, suggesting current definitions need adjustment.
- **PGA Drivers:** PGA is mainly influenced by pain and functional incapacity, with pain accounting for up to 75% of the score, highlighting its clinical significance.

the individual level according to the concepts, wordings/phrasing used, and time period assessed, these differences do not always reflect differences at the group level [11, 12]. Direct comparison between studies is limited due to differences in techniques used to assess the PGA and the population used. Although this has not been explored, it is possible PGA interpretation may be different in clinical trials versus in "clinical practice", in particular given population selection and the often multiple use of PROs in studies. Table 4 summarizes the main aspects of the PGA and key messages presented in this review.

Interpretation of PGA levels for remission

Both DAS28-based remission and ACR/EULAR defined remission criteria incorporate PGA into their scores [2, 35]. ACR/EULAR Boolean-based remission is defined as PGA ≤1 using a 0–10 VAS. Therefore, PGA plays a major role in determining fulfillment of remission criteria in RA [6, 7, 35, 36]. In fact, PGA appears to be often a limiting factor for remission—i.e., in patients with no visible inflammation, remission may not be reached because of PGA. In a study based on the DREAM remission induction cohort, ACR/ EULAR remission was present in 20.1 % of the patients. In 108 out of 512 patients, the PGA score was >1 using a 0– 10 VAS despite fulfillment of the remaining criteria (TJC28, SJC28, and C-reactive protein in mg/dl ≤1). The specific wording of questions and anchors used for the PGA were: "Considering all of the ways your arthritis affects you, mark "X" on the scale for how well you are doing" ("very well" to "very poor")" [37]. Similarly, close to half the patients without visible inflammation in the ESPOIR cohort did not achieve ACR/EULAR remission because of PGA levels above 1/10 cm [38]. Thus, near-remission defined as three of the four criteria (PGA excluded) is the most frequent status [36–39]. Many of these patients have a PGA above 1 but still quite low (usual values are around 2/10) [40], perhaps suggesting a need for revising the remission cutoff value for PGA. Another question relates to the phrasing of PGA in the remission criteria: would using the "disease activity" formulation make more sense than using the "global health" formulation? Unpublished results based on the ESPOIR French early arthritis cohort indicate that the disease activity wording will lead to less states of near-remission.

Overall, the high frequency of near-remission raises the question of whether the way remission is defined needs to be better clarified, i.e., should it reflect absence of inflammation alone or absence of inflammation and symptoms? The current amalgamation of joint counts and C-reactive protein with PGA indeed leads to some difficulties of interpretation, particularly in cases of near-remission. Furthermore, the predictive validity of near-remission is of clear importance, predicting long-term outcomes of these patients. Our unpublished results indicate near-remission predicts radiographic progression over 3 years in early RA, as well as ACR/EULAR remission, in the ESPOIR cohort, suggesting near-remission is a possible valid and even sufficient predictive outcome in early RA [40, 41]. In the context of treating to target, more work is needed on how to best interpret levels of PGA when aiming for remission.

What are the elements explaining PGA?

PGA is a wide-reaching measure which may mean different things for different people. Data are available on the main drivers of PGA at the group level. PGA reflects both disease activity and other factors. Given PGA is assessed to provide information additional to joint counts or acute phase reactants, it is expected there might be some but not complete overlap.

PGA is explained by RA disease activity

Disease activity (i.e., RA inflammatory status) explains a large part of PGA. Pain is a major cause of distress in patients with RA and this, along with joint damage, is among the important aspects/domains of RA that affect patients' lives and will contribute to how the PGA is scored. Most studies indeed support that pain and functional incapacity (evaluated by HAQ), are the most important drivers of PGA, and these outcomes are indirectly reflecting RA disease activity. Furthermore, fatigue plays a role and has also been found to be an important determinant of PGA [13]. However, joint counts and acute phase reactants are not strong drivers of PGA [12, 36]. In several studies pain is the single main driver of PGA and may explain up to 75 % of the PGA result, whether the concept is global health or disease activity [11, 13]. This high contribution from pain is multifactorial but strongly related to the inflammatory status [42]. This probably contributes to its high responsive-

Table 4 Summary of PGA aspects discussed in this review

Aspects covered	Main findings
Description and practical application	Two different concepts covered: global health versus disease activity
	The wording/phrasing and time-reference used remain unstandardized, leading to differences in interpretation and therefore the responses obtained
	There exist different scales to score PGA
Psychometric properties	Practical, feasible, and non-costly to use in routine clinical practice
	High face validity but its broad concept can lead to difficulties with interpretation
	Good reliability and sensitive to change, making it useful in clinical practice and in research
Consequences of heterogeneity	Differences in interpretation of results
	Impact on DAS28 scoring and therefore the achievement of remission
Elements explaining PGA	RA disease activity as indirectly reflected by inflammation, pain, and functional incapacity (partly due to joint damage) and fatigue explain a large component of the PGA
	Psychological distress can result in higher PGA
	Conflicting evidence exists on the impact of comorbidities on PGA
	Non-RA factors impacting on PGA include demographic characteristics, education, culture, and geographic origin
	Differences in patient understanding and interpretation affect the responses
Discordance between PGA and physician global assessment	More objective measures of disease, e.g., joint counts and acute phase reactants lead to a higher physician global assessment whereas pain and altered quality oflife without visible signs of inflammation result in higher PGA
	Patient–physician discordance can affect DAS28 scoring and decision-making, e.g., treatment escalation

Key points

- **Drivers of PGA:** Influenced by disease activity and non-RA factors like demographics and psychological distress, with variations based on wording.
- **Psychological Impact:** Psychological distress significantly affects PGA scores, especially with global health phrasing.
- **Discordance:** Patients often score PGA higher than physician assessments, reflecting a focus on pain and quality of life.
- **Patient-Centered Care:** Incorporating PGA into routine care underscores the importance of patient perspectives in treatment decisions.

ness in trials. We should recognize, however, that pain itself is multifactorial.

With regard to concepts underlying PGA, as expected the disease activity-PGA is more related to inflammation than the global health-PGA. Data from the Quantitative Standard Monitoring of Patients with RA (QUEST-RA) study support that the PGA is explained by different drivers depending on the wording used [12].

PGA is explained by non-RA factors

Over and above disease activity, PGA is affected by other factors, including RA-related factors such as structural damage and non-RA factors such as demographic characteristics, education level, and perhaps culture and geographic origin (Table 1) [36, 43]. Furthermore, interpretation of the question by the patient may depend on duration of disease through a "response shift" resulting from better familiarity with symptoms and changes in patient expectations, as mentioned above.

In the QUEST-RA study, psychological distress was an important driver of PGA and was influenced by the different wording used for the PGA: it was driving more importantly global health than the disease activity wording [13]. There is conflicting evidence on the impact of comorbidities on PGA: a cross-sectional study of US Hispanics with RA showed no association between comorbidities, including depression and fibromyalgia, and PGA [44]. In contrast, based on a study of 50 female patients with RA, in those with co-existing fibromyalgia, significantly higher subjective items, including the PGA (using global health wording) were noted [45]. Differences in the study population and design, as well as the collection and recording of comorbidity data, could account for the variations seen between studies.

Discordance between PGA and physician global assessment

It is interesting to compare PGA to another global, "gestalt" assessment of disease, which is the physician global assessment. Physician global assessment is a well-validated outcome which is recognized as part of the RA core set [3]. Evidence suggests that discordance exists between patient and physician assessment of RA disease activity, with studies consistently showing that PGA is very often scored higher than physician global assessment [13, 43, 46–49]. Discordance in most studies is defined as a difference of ≥3/10 points between the PGA and physician global assessment [12]. The prevalence of discordance using this definition was found to be around 43 % in a recent meta-analysis, indicating a different understanding or perspective of the same general concept [48].

What studies have shown to date is that variables that are important to patients are not the same as those valued by physicians as reflecting disease activity (Table 5). Generally, more objective measures of disease, e.g., joint counts and elevated acute phase reactants, lead to a higher physician global assessment whereas pain and altered quality of life without visible signs of inflammation, but also comorbidities and psychological distress, will lead to higher PGA (Table 5) [50]. In such cases of discordance, it is important to discuss the patient's psychological status as well as personal life factors since the solutions will not always lie in immunosuppressive drugs but rather might depend on non-pharmacological interventions. This discordance may act as a clue to the presence of non-disease severity factors influencing the PGA.

Discussion

The increasing emphasis on the patients' perspective of health in considering priorities and making treatment choices has resulted in PROs being a core part of routine assessment of disease in RA and also an end-point in clinical trials and observational studies. Recent guidelines are characterized by a shift from the traditional approach of physician-led physical examination and investigations such as laboratory tests and radiographs (the "biomedical model") to a more patient-centered approach to care [51]. PGA is one of the most commonly captured and reported PROs, mainly due to its simplicity and its feasibility in both clinical practice and registers as well as in clinical trial settings. It is strongly correlated with other self-reported outcomes and carries important patient information. Therefore, despite the controversy regarding the value of PROs including the PGA, these represent the only way to assess some of the aspects related to RA, for example, symptoms, justifying that clinician-reported outcomes and PROs should be considered as

complementary to each other [52].

The lack of homogeneity in the concepts, wordings/ phrasings, and time period assessed by PGA threatens the validity of PGA since it may lead to modified responses resulting from the diversity of formulations [15]. Such diversity can influence clinical and treatment decision-making, highlighting the importance of standardizing (where appropriate) and validating the question phrasing as part of capturing information on PGA. We suggest that emphasis is placed on reducing heterogeneity in wording/ phrasing and time period of the PGA in order to enable more uniform capture (and hence interpretation) of information across clinical and research settings.

The discordance between PGA and physician global assessment demonstrated in many studies to date suggests that perceptions of disease activity by patients may be influenced by different factors, resulting in different aspects of disease being measured. Such discordance can negatively influence medical care, adherence to treatment, and disease outcomes. Despite this, the use of PROs such as PGA is particularly informative, bringing additional information and perspective, especially given the observed discordance of assessment between physicians and patients [52]. Like other PROs, it is of particular value when changes in clinical measurements or

Key points

Variability in PGA concepts and phrasing can compromise its validity, highlighting the need for standardization to improve patient care and treatment adherence.

Table 5 Discordance between PGA and estimator global assessment and associated factors

Study group	Study description	Patient number (n)	Discordance between PGA and EGA	Factors associated with discordance
Desthieux et al. 2016 [55]	Systematic literature review and meta-analysis	11,879 (12 studies)	Frequency of discordance >2.7 cm (weighted mean cutoff): 44.9 % PGA > EGA: 79.1 % PGA < EGA: 20.9 %	Drivers of global assessment: PGA: pain (the most frequent driver of PGA, significant in eight studies [100 % of studies analyzing this driver of PGA]), functional incapacity, fatigue EGA: swollen and tender joint counts, acute phase reactants Drivers of discordance: Depressive symptoms, health literacy
Davis et al. 2014 [56]	Consecutive RA patients	127	Frequency of discordance: PGA > EGA: 16.5 % PGA < EGA: 10.2 %	PGA > EGA: pain, fatigue, HAQ disability, poor health related quality oflife on the SF-36 PGA < EGA: higher numbers of swollen joints, positive rheumatoid factor and lower pain; better overall physical and mental health
Khan et al. 2012 [13]	Patients from the multi-national Quantitative Standard Monitoring of Patients with RA (QUEST-RA) database	7028	Mean PGA 4.0 ± 2.7 cm; EGA 2.9 ± 2.4 cm Frequency of discordance >2 cm: PGA > EGA: 30 % PGA < EGA: 6.6 %	PGA > EGA: higher age; higher scores of pain, fatigue, HAQ, and morning stiffness PGA < EGA: higher SJC, TJC, ESR; lower fatigue score
Barton et al. 2010 [48]	Multi-site observational cohort with RA adults consecutively enrolled from two outpatient clinics in the US	223	Mean PGA 4.3 ± 2.6 cm; EGA 3.1 ± 2.1 cm Frequency of discordance >2.5 cm: PGA > EGA: 31 % PGA < EGA: 5 %	PGA > EGA: higher HAQ score; lower SJC; greater depressive symptoms
Nicolau G et al. 2004 [43]	Single center cohort of RA patients in Brazil	80	Frequency of discordance≥1 cm: PGA > EGA: 44 % PGA < EGA: 28 % Frequency of discordance≥3 cm PGA > EGA: 24 % PGA < EGA: 9 %	PGA > EGA: higher pain and HAQ scores and tendency for higher number of comorbid conditions
Studenic et al. [42]	Single center observational cohort of RA patients initiating MTX in Austria	646	Mean PGA 3.9 ± 2.7 cm; EGA 2.3 ± 2.1 cm Frequency of discordance≥0.5 cm: PGA > EGA: 61 % PGA < EGA: 15 %	PGA > EGA: higher pain and lower SJC

EGA estimator global assessment, ESR erythrocyte sedimentation rate, HAQ-DI Health Assessment Questionnaire-Damage Index, MID minimally important difference, PGA patient global assessment, SDD smallest detectable difference, TJC tender joint count, SF-36 36-item Short Form Health Survey

Table 6 Proposals of wording/phrasing in view of homogenizing PGA

Concept	Global health	Disease activity
Wording/phrasing	"Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing "	"Considering all the ways your arthritis has affected you, how do you feel your arthritis is today ?"
Scoring	0–100 VAS or 0 –10 NRS	0–100 VAS or 0 –10 NRS Inactive–very
Anchors	Very well–very poorly	active

Key points

PGA is a crucial outcome measure in RA, but its variability in wording, phrasing, and reference periods can lead to misinterpretations; thus, standardizing these elements is essential for accurate assessments and treatment targeting.

laboratory or radiographic outcomes may not translate into meaningful benefits for patients. In particular, the ease of use and feasibility of PGA, with little or no training of patients required to complete it, means that it can be easily incorporated into busy clinical settings. However, it is important that this contribution of patients to disease activity scores via the PGA is evaluated in a standardized way.

We feel the lack of a standardized definition on the concept, wording/phrasing, and time period assessed as part of PGA represents one of its weaknesses. This does not preclude the possibility of having more than one version of PGA; however, it requires clarity with regard to what version is selected and for which purpose (e.g., PGA for disease activity or PGA for global health). We advocate the use of a homogeneous wording in a specific context, e.g., for repeated measures it is important to use the same wording/phrasing. This is particularly important in routine clinical practice since it may lead to incorrect interpretations regarding, for example, response to treatment.

In terms of practical recommendations, the suggestion of the authors is that phrasing of PGA may at this stage be proposed as capturing (1) either global health or disease activity which is (2) related to arthritis and captured by the reference period of (3) today/this point in time. Examples would be the formulation proposed in the RAPID 3 score for global health or the one proposed in the EULAR/ACR remission criteria for disease activity (Table 6) [37].

The choice between the two concepts will depend on the objective of the measurement of the PGA. The global health question gives more holistic information on patient status since it includes to a wider extent elements such as comorbidities and psychological distress. The disease activity-PGA is more in line with more objective measures of disease and assesses more closely the inflammatory burden.

Conclusions

PGA is a key outcome measure in RA with clear validity and usefulness. However, the lack of a "gold standard" in terms of its wording/phrasing and time period assessed necessitates more research into this field in order to avoid pitfalls in interpretation and, consequently, in the achievement of treatment targets. In this review, we propose homogenized wordings which may be considered for future studies. Importantly, a clear understanding of what PGA measures and potential sources of variation in its reporting is key to accurate interpretation. Furthermore, this review gives insights into factors associated with and affecting PGA—for example, its close association with pain, mood, and fatigue and issues around discordance with physician global assessment. This may be informative in guiding interventions to improve care and overall quality of life for RA patients.

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Non-pharmacological and non-surgical interventions to manage patients with knee osteoarthritis: An umbrella review 5-year update

Objective: This umbrella review aimed to summarize (and update) the effectiveness of non-pharmacological and non-surgical interventions for patients with knee osteoarthritis.

Methods: The study followed the PRISMA guidelines. Manual and electronic databases were searched, to identify systematic reviews, following the P (knee osteoarthritis) I (non-pharmacological and non-surgical treatments) C (pharmacological, surgical, placebo, no intervention, or other non-pharmacological/non-surgical conservative treatments) O (pain, function, quality of life, and other knee-specific measures) model. The quality of evidence was assessed using the R-AMSTAR checklist and GRADE principles.

Results: The search yielded 4086 records, of which 61 met the eligibility criteria. After evaluation with RAMSTAR, four systematic reviews were excluded, resulting in 57 included systematic reviews, with an overall score of 29.6. The systematic reviews were published between 2018 and 2022 (29.8% in 2022), conducted in 19 countries (52.6% in China), and explored 24 distinct interventions. The systematic reviews encompassed 714 trials (mean of 13 7.7 studies per systematic review), and 59,343 participants (mean 1041 1002 per systematic review, and 82 59.2 per study). The majority of participants were older obese women (61.6 4.2 years, 30.2 3.6 kg/m2, 70%, respectively).

Conclusions: Based on the systematic reviews findings, Diet Therapy, Patient Education, and Resistance Training are strongly supported as core interventions for managing patients with knee osteoarthritis. Aquatic Therapy, Balance Training, Balneology, Dietary Supplements, Extracorporeal Shockwave Therapy, and Tai Ji show moderate support. For other interventions, the evidence quality was low, results were mixed or inconclusive, or there was not sufficient efficacy to support their use.

1. Introduction

Osteoarthritis (OA) is a non-communicable, chronic, and progressive disease characterized by degenerative changes in the joint [1]. OA can impact various joints, with the knee being the most commonly affected location [2]. The development of knee osteoarthritis (KOA) is often related to many factors, including the patient's age, sex, knee joint trauma, obesity, inflammation, muscle mass, menopausal status, occupational labor intensity, exercise intensity, and genetics [3–5]. The incidence of KOA is increasing annually particularly due to the increased aging population and growing rate of obesity [6]. Given that a significant proportion of OA patients have co-existing medical conditions and co-morbidities, they require special attention due to their fragility [7–9].

ManagingKOAis challenging and impose billions of dollars per year in costs to healthcare systems (could reach 0.25%–0.50% of a country's Gross Domestic Product) [10–12]. Current strategies to manage KOA patients include conservative (pharmacological and/or non-pharmacological) and surgical interventions [13]. Clinical guidelines recommend conservative non-pharmacological interventions asfirst line for managing KOA patients [14–19]. Although the paramount importance of conservative non-pharmacological strategies, only 65 to 40% of patients with KOA receive proper treatment approach [20], indicating that the uptake of evidence-based guidelines in clinical practice and rehabilitation is still suboptimal [21–25]. Instead, surgical and pharmacological strategies remain dominant, despite the fact that use of many of these treatments has been associated with adverse side effects or unnecessary procedures and costs [18].

While there are numerous non-pharmacologic and non-surgical interventions for KOA, and integrated models of patient-centered multidisciplinary care have been shown to improve outcomes, there is no cure or proven strategy for slow, prevent, stop, or reverse the progression from early to end-stage OA [1,23,26,27]. Understanding treatment strategies for KOA is essential for improving rehabilitation outcomes across all stages of management (health promotion; detect and treat early; and reduce the damage) [1,11,23,28–33]. Therefore, continuously updating evidence is essential for optimizing patient care and addressing gaps in knowledge.

There is, to our knowledge, no available update of the last umbrella review [34] on the effectiveness of non-pharmacological and non-surgical interventions for KOA. Therefore, the aim of this study is to summarize and update the available high-quality evidence from systematic reviews on the effectiveness of non-pharmacological and non-surgical interventions for KOA patients.

2. Methods

This review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement[35] (checklist presented in Supplementary Material Table 1). The review protocol was registered prospectively at the PROSPERO (International

Key points

- **Search Strategy:** A systematic search in multiple databases was performed using the P.I.C.O.S. model to find systematic reviews on non-pharmacological and non-surgical treatments for KOA published after January 2018.
- **Eligibility Process:** Two authors independently screened titles and abstracts, including relevant studies on hip and KOA, and removed duplicates before assessing full texts for eligibility.
- **Data Extraction:** Data were collected by one author and verified by another, documenting sample sizes, interventions, outcomes, and conclusions in an Excel spreadsheet.
- **Outcome Measures:** The review focused on pain, function, overall quality of life (QOL), and knee-specific measures (e.g., KOOS, WOMAC), using both qualitative and quantitative synthesis methods.

Prospective Register of Systematic Reviews —www.crd. york.ac. uk/prospero) under identification number CRD42023485026.

2.1. Search strategy

The literature search aimed to identify systematic reviews that evaluated the effect of non-pharmacological and non-surgical interventions for KOA. In January 2024, systematic and comprehensive searches were conducted in electronic databases: PubMed, PEDro, Scopus, EBSCO, The Cochrane Library, Web of Science and Google Scholar. The search strategy was guided using the following patients, intervention, comparison, outcomes, studies (P.I.C.O.S.) model: KOA; non-pharmacological and non-surgical treatments; pharmacological, surgical, placebo, no intervention, or other non-pharmacological/non-surgical conservative treatments; pain, function, quality of life (QOL) and other knee-specific outcomes. For the search strategy, a conjunction of keywords, mesh terms and established search filters were used. The main keywords used to search in the databases were maintained from the previous umbrella review [34], namely: "knee"; "osteoarthritis"; "gonarthosis"; and "systematic review". The terms (and their associates/derivatives) were then combined with the appropriate truncation and Boolean connectors. There was no language restriction. However, considering the last known umbrella review by Ferreira et al. [34], the search was restricted to systematic reviews of non-pharmacological and non-surgical treatments for KOA published in the electronic databases after January 2018. Additional publications that were not found during the original database search were identified through manual searches of the personal, related studies, website bibliographies and references lists. An online search strategy draft used is presented in Supplementary Material Fig. 1.

2.2. Study selection process

Two independent authors conducted the search in the electronic databases and screened the studies' titles and abstracts to determine if they met the established eligible criteria. Considering the biomechanical and disease relationship, systematic reviews exploring both hip and KOA could be included, if the results from patients with KOA could be extracted separately. Potential studies were compiled in EndNote, and the duplicates removed using the automated software command "find duplicates". Beyond this process, all the studies were manually reviewed to ensure that no duplicates remained. The authors then assessed the fulltext versions and decided whether they actually met the eligible criteria. In cases where full versions were inaccessible or data were missing, authors of the respective studies were contacted via email. The study selection process was supervised, and the disagreements were solved through verbal discussion or arbitration by a third reviewer. The inclusion and exclusion criteria applied to this review are similar to the previous umbrella review [34] (Table 1).

2.3. Data extraction and syntheses

Data collection and extraction were performed by one author, with another author verifying the process to enhance consistency. The selected study-associated documents (i.e., full document, supplementary material, appendices, and journal publications) were collected for analysis. The extracted data from the selected publications to assess the effectiveness of non-pharmacological and non-surgical interventions included: title, authors' name, year of publication, KOA conditions, participants' sample size and their characteristics, objectives, description of the interventions, description of the control groups, studies' outcomes, assessment times, studies' results and studies' conclusions. An Excel spreadsheet was created for a proper data analysis.

2.4. Outcomes

Studies were combined using the most adequate qualitative and quantitative evidence synthesis, and maintained most of the previous umbrella terms, such as pain, function, overall QOL, knee-specific outcomes measures (e.g., KOOS [Knee injury and Osteoarthritis Outcome Score], and WOMAC [Western Ontario and McMaster Universities Arthritis Index]), and other knee-related outcomes (e.g., inflammatory markers, and radiological findings).

2.5. Quality assessment

Two authors independently assessed the risk of bias, while a third author arbitrated when needed. The reviews were evaluated using

Table 1
Inclusion and Exclusion criteria.

Inclusion	Exclusion
at least one of the keywords;	papers with experimental or control group composed by any kind of animal;
papers with an intervention group that has primary KOA either clinical or radiological criteria (or a combination);	papers with participants that do not have a KOA (healthy subjects) or who have secondary KOA (traumatic or post-surgical);
with or without meta-analysis, exclusively from randomized controlled trials, after January 2018;	with or without meta-analysis of randomized controlled trials prior to January 2018;
papers with non-pharmacological and non-surgical interventions;	papers with multi-modal interventions or exclusively surgical, pharmacological (injectable, topical, oral, or inhalation), or herbal interventions;
with their full versions, published in peer-reviewed scientific literature journals;	books, controlled trials, case reports, expert opinions, conference papers or academic thesis;
papers that evaluate pain, function, overall QOL, or other knee-related symptoms and measures;	papers with subjects with other illnesses namely cancer, heart diseases, kidney diseases, neurological diseases, respiratory diseases, rheumatoid arthritis, gouty arthritis, septic arthritis or Paget's disease;
detailed description of the non-pharmacological and non-surgical intervention;	papers with subjects exclusively with osteoarthritis in the hip, foot, shoulder, elbow, wrist and/or fingers.
performed under the PRISMA guidelines;	
studies that exhibit the highest specificity within each identified intervention MeSH term.	

the R-AMSTAR (Revised A MeaSurement Tool to Assess systematic Reviews) 11-item checklist [36]. In R-AMSTAR each domain's score ranges between 1 (minimum) and 4 (maximum), and the total score has a range of 11 (minimum) to 44 (maximum). Based on the overall score, quality grades are assigned as follows: A (high quality: 44-33 score); B (moderate quality: 32-23 score); C (low quality: 22-13 score); and D (very low quality: 12-11 score). Considering the recommendations that only total scores of 23/44 are considered to have at least moderate methodological quality, it was established as the cutting-point for include a systematic review in this study.

Additionally, GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guidelines [37–41] were adapted, following the same principles as Jamtvedt et al. [42], to assess and integrate the strength of evidence for each intervention (Table 2).

3. Results

As umbrella reviews are designed to provide an overview of the topic appraised, the results of the search will be presented in the Results section. The conclusions and orientations of the individual papers will be summarized by treatment domain in the Discussion section, with further details provided in a tabular form (Table 4).

3.1. Selection of the studies

The searches yielded 4086 records, out of which 930 were screened. After the application of the inclusion and exclusion criteria, 57 could be included. The flowdiagram (Fig. 1) and the Supplementary Material Table 2 summarizes the selection process. 3.2. Methodological quality The methodological quality assessment revealed a mean score of 29.1 (range 21–39) [43–103]. Among the assessed studies, the two problematical items were the list of studies, and the of publication bias assessment. The domains characteristics of the included studies, and conflict

Key points

- **R-AMSTAR and Study Selection:** The R-AMSTAR checklist scores systematic reviews from 11 to 44, with a cutoff of 23 for inclusion. Out of 4086 screened records, 57 studies were included, yielding a mean methodological quality score of 29.1 (range 21–39). Issues were noted in study listing and publication bias assessment.

Table 2
Grading quality of evidence.

Level	Criteria
High-quality evidence (A) (Highly recommended)	One or more high-quality systematic review that are based on at least 2 high-quality primary studies with consistent results
Moderate-quality evidence (B) (Moderately recommended)	One or more systematic reviews of high or moderate quality • Based on at least 1 high-quality primary study • Based on at least 2 primary studies of moderate quality with consistent results
Low-quality evidence (C) (Uncertainty)	One or more systematic reviews of high or moderate quality • Based on primary studies of moderate quality • Based on inconsistent or conflicting results in the reviews • Based on inconsistent or conflicting results in primary studies
Very low-quality evidence (D) (No recommendation)	No high-quality systematic review identified or supports the intervention

Key points

Fifty-seven systematic reviews (2018–2022) focused on non-pharmacological and non-surgical interventions for knee osteoarthritis, primarily from China (52.6%). They analyzed 714 trials with 59,343 participants (70% female). Key outcomes included pain (31.6%) and physical function (27.1%). Each review covered an average of 7.3 years of research.

of interest were less problematic items. Four systematic reviews [61,74,79,90] were excluded because they did not reach 23/44, raising the mean score to 29.6. The classifications obtained are described in Table 3.

3.3. Study characteristics

The 57 reviews included [43–60,62–73,75–78,80–89,91–103] were published from 2018 [45,46,52,55,68,75] to 2022 [43,44,48,49,59,64, 73,76,80,82,83,87–89,96–98], being 2022 the most common year (17; 29.8%). The reviews were conducted in 19 different countries, majorly in China [48–51,55,57,59,62,63,68–73,75,76,82,86,89,94,96–103] (30; 52.6%), followed by India [78,87,92] and Australia [56,60,66] (each with three; 5.3%). Supplemental Figures 2 and 3, show in more detail the years and countries distribution.

The reviews encompassed a total of 714 clinical trials, yielding a mean of 13 7.7 studies per review (maximum: 50 [70]; minimum: 3 [81]). The number of participants enrolled in the studies was 59,343, averaging 1041 1002 per review (maximum: 4844 [70]; minimum: 117 [81]), and 82 59.2 (maximum: 336 [84]; minimum: 15 [68]) per RCT. Among these participants, approximately 70% were female (male [n,%] – maximum: 1500 [56], 60% [43]; minimum: 17 [81], 3.5% [72]; female [n,%] – maximum: 3787 [70], 96.5% [72]; minimum: 100 [81], 40% [43]), with a mean BMI of 30.2 3.6 (maximum: 40 [60]; minimum: 23 [70]) and 61.6 4.2 years of age (maximum: 74.1 [66]; minimum: 53.4 [95]). The most frequently reported outcomes were physical function (27.1%; e.g., ROM, strength, TUG, and 6MWT), pain (31.6%; e.g., VAS and NPRS), and knee-specific patient-reported (32.9%; e.g., WOMAC and KOOS) related. QOL (e.g., SF-36), radiological (e.g., X-ray), and laboratorial (e.g., erythrocyte sediment rate) outcomes, accounted for only 5.2%, 1.9%, and 1.3%, respectively. The systematic reviews explored 24 distinct non-pharmacological and non-surgical interventions (Fig. 2).

From the individual studies included in the reviews, 43 countries were enlisted, being China (19.4%) and USA (15.4%) the most prominently represented countries. On average, each review covered 6 2.8 countries, with Liao et al. [69] including the most countries (13) and Zeng et al. [103] being the less international (100% China). The years ranged 1974–2022, with the most common years being 2012 (5.8%), 2013 (5.6%), 2014 (5.5%), 2015 (6.2%), 2016 (12.4%), 2017 (11.3%), 2018 (11%), and 2019 (6.8%). On average, each review covered 7.3 2.7 years, with Goff et al. [56], Liao et al. [69], and Gong et al. [57] having the widest distribution (13 different years), and Lu et al. [75] and Pitsillides et al. [81] having the narrowest distribution (3 different years). Supplemental Figures 4 and 5, show in more detail the years and countries distribution. The characteristics of

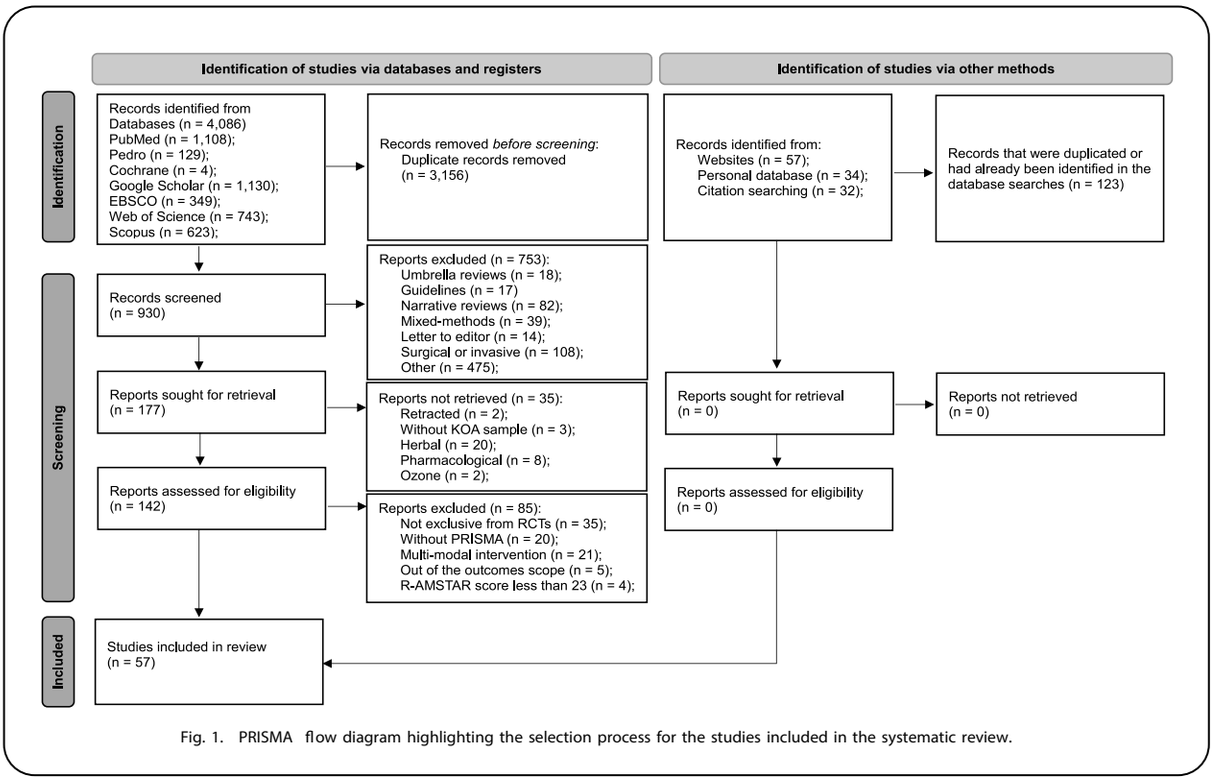


Fig. 1. PRISMA flow diagram highlighting the selection process for the studies included in the systematic review.

the included reviews are summarized in Table 4.

4. Discussion

The discussion will be presented according to the interventions explored in the selected reviews.

4.1. Athletic tape

Among the different taping techniques, Kinesio Tape (KT) was the only analyzed in the reviews [68,72,75,77,96,101]. Apparently, KT can mitigate pain, enhance function, improve self-reported knee-related health status, and increase knee ROM, in short-term [68,72,75,77,96,101]. Notably, no significant differences were observed in strength-related outcomes [68,75, 101]. The evidence suggests a higher degree of certainty regarding the positive impact on pain reduction, particularly when compared with placebo, sham, or no intervention groups [68,75,77,96,101]. Also, combining KT with physical therapy appears to yield superior results compared to physical therapy alone, although additional validation is warranted [72, 101]. Despite these findings, a consensus regarding optimal taping methods remains elusive. Notably, employing a Y-shaped configuration with a 120–140% stretching length over a period of 3–4 weeks has been identified as optimal [72,96]. This technique is believed to stimulate the quadriceps femoris and stabilize the patella, by wrapping the tape around it [72]. However, due to the taping methods heterogeneity among the individual studies (such as taping shape, number of tapes, and different intervention durations) [68,72,75,77,96,101], providing definitive clinical guidance proves challenging, and irrefutable conclusions or recommendations are difficult to achieve. By some methodological inconsistencies in the studies and the overall low-level evidence, this intervention is considered as C.

4.2. Balneology

Based on the reviews [45,62], balneology interventions (particularly those involving mud-related therapies) demonstrate significant efficacy in promptly alleviating pain and improving joint function in the short-term. This pain reduction is highlighted by a significant NSAIDs consumption reduction among

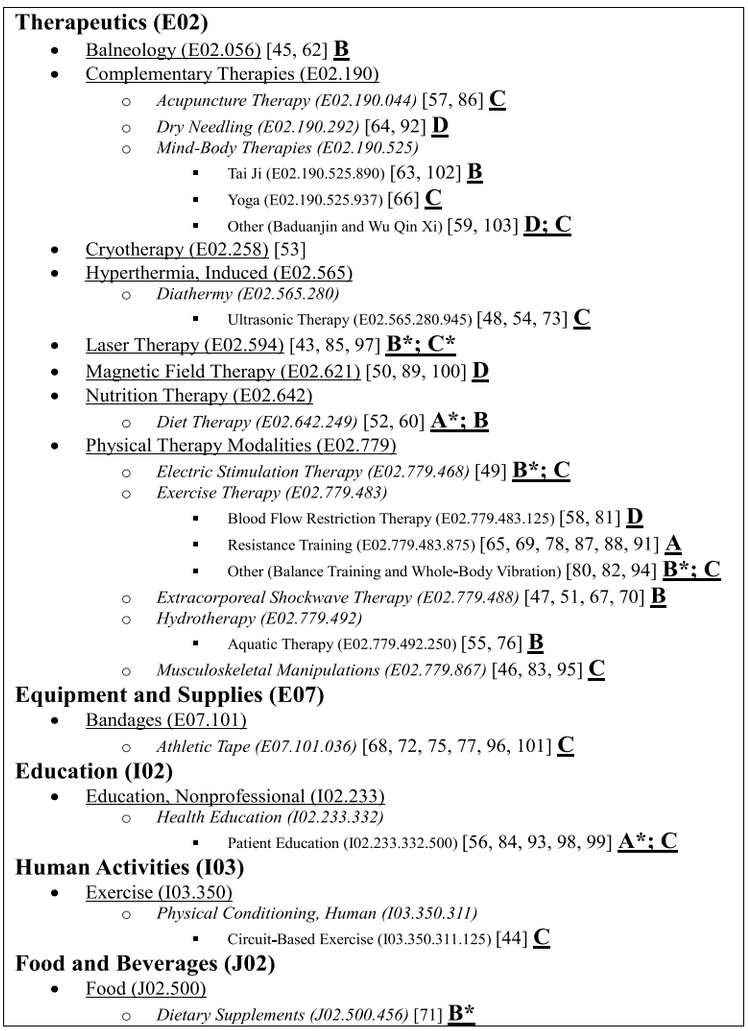
Key points

- Athletic Tape
  Kinesio Tape (KT) is effective for short-term pain reduction, improved function, and knee ROM, but not strength. While combining KT with physical therapy may enhance results, vary ing methodologies in studies complicate definitive recommendations,classifying this as low-level evidence (C).
- Balneology
  Mud-related balneology therapies effectively reduce pain and improve joint funtion in the short term.

Table 3
Methodological quality of eligible studies (n ¼ 61).

Study (Author; Year)	R-AMSTAR Items											R-AMSTAR	Grade
	1	2	3	4	5	6	7	8	9	10	11	Score (11– 44)	(A –D)
Ahmad et al. [43]	3	4	4	2	4	4	2	3	2	1	3	32	B
Al-Mhanna et al. [44]	3	4	1	2	1	3	4	4	1	1	4	28	B
Antonelli et al. [45]	3	4	4	2	1	3	4	1	2	1	3	28	B
Anwer et al. [46]	3	4	4	2	1	4	2	3	2	1	3	29	B
Avendano-Coy et al. [47]	3	4	4	2	2	4	4	3	4	2	4	36	A
Chen et al. [48]	4	2	4	3	2	4	3	2	4	1	3	32	B
Chen et al. [49]	4	4	4	3	1	4	3	2	1	1	4	31	B
Chen et al. [50]	3	4	4	2	1	4	3	2	4	1	4	32	B
Chen et al. [51]	3	4	3	3	1	3	3	2	3	3	4	32	B
Chu et al. [52]	3	1	4	2	1	3	3	3	1	1	2	24	B
Dantas et al. [53]	3	4	3	3	1	4	4	1	1	1	4	29	B
Dantas et al. [54]	3	4	4	2	1	3	4	4	2	1	4	32	B
Dong et al. [55]	3	4	3	2	1	3	3	1	2	1	4	27	B
Goff et al. [56]	3	4	4	3	3	4	3	3	4	2	4	37	A
Gong et al. [57]	3	2	3	2	1	3	3	1	2	2	4	26	B
Grantham et al. [58]	4	1	4	2	2	4	4	4	3	1	4	33	A
Guo et al. [59]	3	2	2	2	1	4	3	2	3	1	4	27	B
Hall et al. [60]	3	4	4	3	2	4	4	3	3	2	2	34	A
Heddon et al. [61]	3	2	3	2	1	1	3	1	1	1	4	22	C
Hou et al. [62]	2	4	3	2	1	2	3	1	2	2	4	26	B
Hu et al. [63]	3	4	3	2	1	3	4	2	2	1	4	29	B
Jim énez-del-Barrio et al. [64	4	4	4	2	1	4	4	3	1	2	4	33	A
Kus and Yeldan [65]	3	2	3	2	1	4	3	2	1	1	1	23	B
Lauche et al. [66]	3	4	4	3	3	3	4	4	1	1	2	32	B
Li et al. [67]	3	2	3	2	1	2	2	1	2	1	4	23	B
Li et al. [68]	3	4	4	3	2	4	4	1	1	2	2	30	B
Liao et al. [69]	3	4	4	3	2	4	3	3	3	3	1	33	A
Liao et al. [70]	3	4	4	3	1	3	3	1	4	2	4	32	B
Liao et al. [71]	3	4	2	2	1	4	2	2	2	2	4	28	B
Lin et al. [72]	3	4	4	3	4	3	3	2	2	2	4	34	A
Liu et al. [73]	2	4	3	2	1	4	3	1	1	1	2	24	B
Long et al. [74]	3	2	1	3	1	3	3	1	2	2	1	22	C
Lu et al. [75]	3	4	4	2	1	4	3	2	3	1	4	31	B
Ma et al. [76]	3	4	4	2	1	3	3	2	2	1	4	29	B
Melese et al. [77]	3	4	3	2	1	3	4	1	1	1	3	26	B
Neelapala et al. [78]	3	3	4	2	2	4	3	3	1	1	1	27	B
Novak et al. [79]	3	2	2	2	1	3	3	1	1	1	2	21	C
Pirayeh et al. [80]	3	4	2	2	1	4	4	1	1	1	2	25	B
Pitsillides et al. [81]	2	1	4	2	4	4	2	3	1	1	3	27	B
Qiu et al. [82]	3	4	2	2	1	3	3	2	1	1	4	26	B
Runge et al. [83]	3	2	4	3	1	3	4	4	3	1	2	30	B
Safari et al. [84]	4	4	4	2	4	2	4	2	1	1	4	32	B
Stausholm et al. [85]	2	4	3	3	3	4	3	2	2	1	2	29	B
Sun et al. [86]	2	4	2	2	1	3	2	2	1	1	4	24	B
Thomas et al. [87]	4	4	3	2	1	4	3	2	3	1	4	31	B
Thorlund et al. [88]	3	4	4	3	4	4	4	2	4	3	4	39	A
Tong et al. [89]	3	2	3	2	1	1	3	1	2	2	4	24	B
Tsokanos et al. [90]	2	1	2	3	1	3	3	1	1	1	4	22	C
Turner et al. [91]	3	4	4	3	1	4	3	2	1	1	3	29	B
Ughreja and Prem [92]	2	4	4	2	4	4	3	3	2	1	4	33	A
Uritani et al. [93]	4	4	4	3	2	4	3	2	1	1	4	32	B
Wang et al. [94]	3	4	4	2	1	4	4	4	3	3	3	35	A
Weleslassie et al. [95]	4	2	2	2	1	4	3	2	1	1	2	24	B
Wu et al. [96]	4	4	4	3	4	3	3	2	3	2	4	36	A
Wu et al. [97]	3	2	2	3	1	4	3	2	2	1	4	27	B
Wu et al. [98]	4	3	2	2	1	4	4	3	2	2	4	31	B
Xie et al. [99]	4	3	4	2	1	3	3	2	2	1	4	29	B
Yang et al. [100]	4	4	3	2	1	3	4	1	2	1	4	29	B
Ye et al. [101]	3	2	3	2	1	2	3	1	2	1	4	24	B
You et al. [102]	1	4	4	2	1	3	4	2	3	1	4	29	B
Zeng et al. [103]	3	4	4	3	2	4	3	4	2	2	4	35	A
Average	3	3.3	3.3	2.3	1.6	3.4	3.2	2.1	2.0	1.4	3.3	29.1	B

R-AMSTAR items: 1 – Was an "a priori" design provided?; 2 – Was there duplicate study selection and data extraction?; 3 – Was a comprehensive literature search performed?; 4 – Was the status of publication used as an inclusion criterion?; 5 – Was a list of studies provided?; 6 – Were the characteristics of the included studies provided?; 7 – Was the scienti fic quality of the included studies assessed and documented?; 8 – Was the scienti fic quality of the included studies used appropriately in formulating conclusions?; 9 – Were the methods used to combine the findings of studies appropriate?; 10 – Was the likelihood of publication bias assessed?; 11 – Was the conflict ofinterest included?.



Therapeutics (E02)

- Balneology (E02.056) [45, 62] **B**
- Complementary Therapies (E02.190)
  - *Acupuncture Therapy (E02.190.044)* [57, 86] **C**
  - *Dry Needling (E02.190.292)* [64, 92] **D**
  - *Mind-Body Therapies (E02.190.525)*
    - Tai Ji (E02.190.525.890) [63, 102] **B**
    - Yoga (E02.190.525.937) [66] **C**
    - Other (Baduanjin and Wu Qin Xi) [59, 103] **D; C**
- Cryotherapy (E02.258) [53]
- Hyperthermia, Induced (E02.565)
  - *Diathermy (E02.565.280)*
    - Ultrasonic Therapy (E02.565.280.945) [48, 54, 73] **C**
- Laser Therapy (E02.594) [43, 85, 97] **B*; C***
- Magnetic Field Therapy (E02.621) [50, 89, 100] **D**
- Nutrition Therapy (E02.642)
  - *Diet Therapy (E02.642.249)* [52, 60] **A*; B**
- Physical Therapy Modalities (E02.779)
  - *Electric Stimulation Therapy (E02.779.468)* [49] **B*; C**
  - *Exercise Therapy (E02.779.483)*
    - Blood Flow Restriction Therapy (E02.779.483.125) [58, 81] **D**
    - Resistance Training (E02.779.483.875) [65, 69, 78, 87, 88, 91] **A**
    - Other (Balance Training and Whole-Body Vibration) [80, 82, 94] **B*; C**
  - *Extracorporeal Shockwave Therapy (E02.779.488)* [47, 51, 67, 70] **B**
  - *Hydrotherapy (E02.779.492)*
    - Aquatic Therapy (E02.779.492.250) [55, 76] **B**
  - *Musculoskeletal Manipulations (E02.779.867)* [46, 83, 95] **C**

Equipment and Supplies (E07)

- Bandages (E07.101)
  - *Athletic Tape (E07.101.036)* [68, 72, 75, 77, 96, 101] **C**

Education (I02)

- Education, Nonprofessional (I02.233)
  - *Health Education (I02.233.332)*
    - Patient Education (I02.233.332.500) [56, 84, 93, 98, 99] **A*; C**

Human Activities (I03)

- Exercise (I03.350)
  - *Physical Conditioning, Human (I03.350.311)*
    - Circuit-Based Exercise (I03.350.311.125) [44] **C**

Food and Beverages (J02)

- Food (J02.500)
  - *Dietary Supplements (J02.500.456)* [71] **B***

Fig. 2. The non-pharmacological and non-surgical interventions tree MeSH codes and their hierarchy (n = 57). Note: The letters in bold and underlined are the interventions classification. The "*" symbolize the classi fication when the intervention is added to exercise.

Table 4
Systematic Reviews summaries (n= 57).

Interventions	Authors (A to Z; year)	No of included RCTs (subjects; grade)	Results/Conclusions
Athletic tape			
	Li et al. [68]	11 (n = 168; B)	Statistical significance was found in self-reported pain during activity (MD = −0.85; 95% CI: −1.55 to 0.14; p = 0.02), knee flexibility (MD = 7.59; 95% CI: 0.61 to 14.57; p = 0.03), knee-related health status (WOMAC scale, MD 4.10; 95% CI: 7.75 to 0.45; p = 0.03), and proprioceptive sensibility (MD 4.69; 95% CI: 7.75 to 1.63 ; p = 0.003). However, no significant enhancement was reported regarding knee muscle strength (MD = 1.25; 95% CI: 0.03 to 2.53; p = 0.06).
	Lin et al. [72]	15 (n = 546; A)	The study suggests that physical therapy combined with kinesio taping is more effective than physical therapy alone, as indicated by a greater reduction in pain scores (MD = −0.70; 95% CI: −1.14 to −0.26; p= 0.002) and functional improvement (MD = −5.45; 95% CI: −10.23 to −0.66; p = 0.03). The results also show significant pain reduction (MD = −0.72; 95% CI: −1.18 to −0.26; p = 0.002) and functional improvement (MD = −6.05; 95% CI: −11.18 to −0.93; p = 0.02) within six weeks after initial treatments.
	Lu et al. [75]	5 (n = 363; B)	Kinesio taping is effective in improving for pain (VAS at rest, WMD = −0.394; 95% CI: −0.759 to −0.029; p= 0.034; VAS during walking, WMD = −0.429; 95% CI: −0.752 to −0.105; p = 0.009), WOMAC index score (WMD = −5.026; 95% CI: −7.649 to −2.403; p < 0.001), and knee flexion ROM (WMD = 6.193; 95% CI: 2.678 to 9.709; p = 0.001). However, it does not improve muscle strenght (WMD = 3.205; 95% CI: 3.141 to 9.550; p = 0.322).
	Melese et al. [77]	18 (n = 876; B)	Differences were found between Kinesio Taping groups and control groups in terms of VAS, WOMAC index scale and flexion ROM.
	Wu et al. [96]	16 (n = 642; A)	Therewasa significant difference between the Kinesio taping plus exercise group and the exercise-only group in terms of VAS score after the intervention (MD 0.8 6; 95% CI: 1.32 to 0.40; p = 0.0003). However, no significant differences were found in terms of VAS at the follow-up period (MD 0.58; 95% CI: 1.41 to 0. 25; p = 0.17), WOMAC score (MD = 0.28; 95% CI: 9.16 to 9.71; p = 0.95), and TUG after the intervention (MD 0.74; 9 5% CI: 1.72 to 0 .24; p = 0.1 4).
	Ye et al. [101]	11 (n = 490; B)	The study found statistically significant differences in pain (SMD 0.78; 9 5 % CI: 1.07 to 0.50; p < 0.00001), physical function (SMD = 0.73; 95% CI: 1.03 to 0.43; p < 0.00001), ROM (MD = 2.04; 95% CI: 0.14 to 3.94; p = 0.04), and quadriceps muscle strength (MD = 2.42; 95% CI: 1.09 to 3.74; p = 0.0004). No significant differences were found for the hamstring muscle strength.
Balneology			
	Antonelli et al. [45]	17 (n = 1599; B)	When comparingbalneological interventions with standard treatment, the results showed that the former were more effective in terms oflong-term overall QOL (MD1.03; 95% CI:= −1.66 to 0.40; p < 0.00001). Additionally, when comparing balneological interventions with sham interventions, the results showed that the former were more effective in terms oflong-term pain improvement (SMD= −0.38; 95% CI: 0.74 to 0.02;– p = 0.04), while no significant difference was found when considering social function (SMD = −0.16; 95% CI: −0.52 to 0.19; p = 0.36).
	Hou et al. [62]	11 (n = 1106; B)	The study found significant differences in VAS score (SMD = −0.74; 95% CI: −1.08 to −0.41; p < 0.0001) and WOMAC Index (pain, SMD = −0.53; 95% CI: −0.71 to −0.36; p < 0.00001; stiffness, SMD = −0.50; 95% CI: −0.68 to −0.31; p < 0.00001; function, SMD = −0.43; 95% CI: −0.57 to −0.29; p < 0.00001).
Exercise therapies			
Aquatic therapy	Dong et al. [55]	8 (n = 579; B)	The study found no significant difference in pain relief, physical function, and improvement in QOL between aquatic exercise and land-based exercise for short- and long-term interventions in patients with KOA. However, patients reported higher adherence and satisfaction levels with aquatic exercise compared to land-based exercise. Compared to no intervention, aquatic exercise had a mild effect on elevating activities of daily living (SMD 0.55 ; 95% CI: 0.94 to 0.16; p = 0.005) and a high effect on improving sports and recreational activities (SMD 1.03; 95% CI: 1.82 to 0.25; p =0.01). Aquaticphysical therapy hasbeen foundtosignificantly reduce pain based on the WOMAC index (SMD
	Ma et al. [76]	13 (n = 883; B)	1.09; 95% CI: 1.97 to 0.21; p = 0.02) and VAS (SMD 0.55; 95% CI: 0.98 to 0.12; p =0. 01). Additionally, it effectively improved physical function based on the WOMAC physical function score (SMD 0.57; 95% CI: 1.14 to 0.01; p= 0.05). However, there were no significant improvements in joint symptoms, QOL, flexibility, or body composition for KOA. Aquatic physical therapy has been found to improve knee extension muscle strength (MD = 2.11; 95% CI: 0.02 to 4.20; p ¼ 0.05) and TUG (MD 0.89; 95% CI: 1.25 to 0.53; p < 0.05), thereby improving walking ability.

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Table 4 (continued)

Interventions	Authors (A to Z; year)	No of included RCTs (subjects; grade)	Results/Conclusions
Balance training	Pirayeh et al. [80]	15 (n = 919; B)	The studies revealed that balance training can significantly improve physical function in KOA patients. However, the effect of balance training on muscle strength of the quadriceps and the hamstring remains unclear due to conflicting results. Additionally, the balance training group showed more significant improvement in postural stability and balance compared to the control group.
	Wang et al. [94]	24 (n = 1275; A)	In comparison with no intervention, proprioceptive training significantly improved pain, stiffness, physical function, joint position sense, muscle strength, mobility, and knee ROM (P < 0.05) in people with KOA. When compared to other non-proprioceptive training, proprioceptive training yielded superior results in terms ofjoint position sense (SMD 1.28; 95% CI: 1.64 to 0.92; p <-0.00001) and mobility (timed-walk over spongy surface) (SMD 0.76; 95% CI: 1.33 to 0.18; p = 0.01), while other outcomes were comparable. When comparing proprioceptive training plus other non-proprioceptive training to other non-proprioceptive training, both groups showed similar outcomes. However, the proprioceptive training group showed greater improvement in joint position sense (SMD 1.54; 95% CI: 2.74 to 0.34; p = 0.01), physical function (SMD -0.34; 95% CI: 0.56 to 0.12; p = 0.003), and knee ROM (p < 0.05). When comparing proprioceptive training plus conventional physiotherapy to conventional physiotherapy alone, both groups demonstrated similar outcomes. However, the proprioceptive training plus conventional physiotherapy group showed a significant improvement in joint position sense (SMD 0.95; 95% CI: 1.73 to 0.18; p = 0.02).
Blood flow restriction therapy	Grantham et al. [58]	5 (n = 199; A)	There was no statistical difference (p: 0.329–0.880) found between blood flow restriction therapy and traditional resistance training in terms of pain reduction, functional improvement, and TUG improvement.
	Pitsillides et al. [81]	3 (n = 117; B)	Thebloodflow restriction and high intensity training groups demonstrated significant improvements in quadriceps strength in the strength outcome, with an increase from baseline to post-intervention. Additionally, the blood flow restriction and high intensity training groups showed significant strength gains in leg press and leg extension exercises, while the low intensity training group showed minimal improvements. In terms of the pain outcome, all groups experienced a reduction in pain. However, blood flow restriction training was found to be more effective in reducing compared to high-intensity training. While blood flow restriction resulted in decreased scores on physical function scales compared to baseline, there were no significant changes observed in the TUG test among the three groups. Regarding the QOL outcome, there were few studies to draw conclusions from. However, it appears that all three groups can improve WOMAC scores, with no statistically significant differences found in SF-36.
Circuit-based exercise	Al-Mhanna et al. [44]	7 (n = 346; B)	Theinterventiongroupshowedasignificant improvement in pain level (SMD 0.96; 95% CI: 1.77 to 0.14; p = 0.02). However, no significant improvement was found in physical function (SMD = 0.03; 95% CI: 0.44 to 0.50; p = 0.89), QOL (SMD 0.25; 95% CI: 1.18 to 0.68; p = 0.60), activity of daily living (SMD = 0.81; 95% CI: 0.85 to 2.48; p = 0.34), or knee stiffness (SMD 0.65, 95% CI: 1.96 to 0.66; p = 0.33).
Resistance training	Kus and Yeldan [65]	10 (n = 759; B)	When comparingdifferent exercises to strengthen the quadriceps femoris muscle, no significant difference was found between the training groups. However, exercise training to strengthen the quadriceps femoris muscle was found to be superior to proprioceptive training. Additionally, the use of hot packs along with shortwave diathermy, ultrasound, or transcutaneous electrical nerve stimulation was found to be superior to isokinetic strengthening of the quadriceps femoris muscle alone. Only the additional use of Russian electrical stimulation showed a significant difference compared to the strengthening of the quadriceps femoris muscle exercise. Most of the studies included in this analysis showed that exercises aimed at strengthening the quadriceps femoris muscle have a positive effect on reducing pain and improving function.
	Liao et al. [69]	19 (n = 1195; A)	Musclestrength exercisetrainingresultedin a significantly higher gain in lean mass (SMD = 0.49; 95%CI: 0.28 to 0.71; p < 0.00001), muscle thickness (SMD = 0.82; 95% CI: 0.20 to 1.43; p = 0.009), and cross-sectional area (SMD = 0.80; 95% CI: 0.25 to 1.35; p = 0.004) compared to non-exercise controls. No significant effects in favor of muscle strength exercise training were observed for any muscle outcome compared to exercise controls.
	Neelapala et al. [78]	5 (n = 331; B)	Strong, high-quality evidence demonstrated the effectiveness of hipmuscle strengtheningwas assessed in isolation, combination, and comparison with other lower extremity exercise. Overall, the studies reported clear benefits of hip muscle strengthening on knee pain, physical function, and hip muscle strength. However, hip muscle strengthening was ineffective in improving the biomechanical measures such as dynamic alignment and knee adduction moment.

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Table 4 (continued)

Interventions	Authors (A to Z; year)	No of included RCTs (subjects; grade) 7	Results/Conclusions
	Thomas et al. [87]	(n = 428; B)	Hip abductor strengthening interventions were found to be superior to the control groups. Specifically, hip abductor strengthening signi ficantly reduced the VAS (SMD = −0.60; 95% CI: −0.88 to −0.33; p < 0.0001) and improved the WOMAC scores (SMD = −0.75; 95% CI: −1.05 to −0.45; p < 0.0001). All of the included studies concluded that strengthening the hip abductor muscle had a positive impact on knee pain and functional outcomes.
	Thorlund et al. [88]	13 (n = 1398; A)	The study found that the treatment effect of NSAIDs for KOA pain was comparable to that of opioids (SMD = 0.02; 95% CI: 0.14 to 0.18), Exercise therapy had a larger effect than NSAIDs (SMD= 0.54; 95% CI: 0.19 to 0.89). No estimate could be made for exercise vs opioids due to the lack of studies. Resistance training has
	Turner et al. [91]	12 (n = 1428; B)	been shown to improve pain, QOL, and physical function in individuals with KOA. The study found that 24 total sessions over an 8- to 12-week period had large effect sizes. No optimal number of repetitions, maximum strength, or frequency of sets or repetitions was found. Whole-body vibration combined with
Whole-body vibration	Qiu et al. [82]	14 (n = 559; B)	strengthening exercises has a significant positive effect on pain score (SMD = 0.46; 95% CI: 0.20 to 0.71; p = 0.0004), WOMAC Index (WOMAC-function, SMD = 0.51; 95% CI: 0.27 to 0.75; p < 0.0001), TUG (SMD = 0.82; 95% CI: 0.46 to 1.18; p < 0.00001), extensor isokinetic peak torque (SMD = 0.65; 95% CI: 0.00 to 1.29; p = 0.05), peak power (SMD = 0.68; 95% CI: 0.26 to 1.10; p= 0.001), and extensor isometric strength (SMD = 0.44; 95% CI: 0.13 to 0.75; p = 0.006). Both low-frequency (10 –30 Hz) and high-frequency (30 –40 Hz) whole-body vibration resulted in significant changes in pain, physical function, and knee extensor strength (p < 0.05). Whole-body vibration was not associated with signi ficant changes in stiffness, balance, QOL, and knee flexor strength.
Mind-body therapies			
Baduanjin	Zeng et al. [103]	7 (n = 424; A)	Statistically significant differences were found between Baduanjin exercise and waiting list control on WOMAC index scores (pain, MD 4.40; 95% CI: 7.16 to 1.64; p < 0.01; stiffness, M D 1.34; 95% CI: 1.64, 1.04; p < 0.01; function, MD 2.44; 95% CI: 4.33 to 0.55; p < 0.01). Furthermore, when used in isolation, the Baduanjin exercise demonstrated a statistically significant improvement on three domains of WOMAC index scores (pain, MD 1.69; 95 % CI: 2.03 to 1.35; p < 0.01; stiffness, MD 0.86; 95 % CI: 1.13 to 0.58; p < 0.01; function, MD 2.23; 95 % CI:
			−3.65 to 0.82; p < 0.01) compared to health education. In addition, the combination of Baduanjin exercise and NSAID therapies led to a signi ficant improvement in the total WOMAC score (MD = 10.26; 95% CI: 13.41 to 7.11; p < 0.01) and a reduction in VAS (MD 1.65; 95% CI: 1.83 to 1.48; p < 0.01) compared to NSAID therapies alone.
Tai Ji	Hu et al. [63]	16 (n = 986; B)	Tai Ji significantly improved patients' outcomes, including pain (SMD 0.69; 95% CI: 0.95 to 0.44; p < 0.001), stiffness (SMD 0.59; 95% CI: 0.91 to 0.27, p < 0.001), physical function (SMD =
			0.92; 95% CI: −1.16 to −0.69, p < 0.001), dynamic balance (SMD = 0.69; 95% CI: 0.38 to 0.99; P <
	You et al. [102]	11 (n = 603; B)	0.001), and physiological and psychological health (SF-36 physical, SMD = 0.48; 95% CI: 0.28 to 0.68; p < 0.001; SF-36 mental, SMD = 0.26; 95% CI: 0.06 to 0.45; p = 0.01). The results showed that the Tai Ji group was associated with better performance in 6-MWT (MD = 46.67; 95% CI: 36.91 to 56.43; p< 0.001), TUG (MD 0.89; 95% CI: 1.16 to 0.61; p < 0.001]), and WOMAC Index function score (MD 11.28; 95% CI: 13.33 to 9.24; p < 0.001) than the control group.
Wu Qin Xi	Guo et al. [59]	7 (n= 668; B)	Wu Qin Xi exercise showed a significant improvement in WOMAC total score regardless of the intervention of control group (MD = −105.76; 95% CI: −161.38 to −50.14; p < 0.01). Furthermore, Wu Qin Xi exercise signi ficantly improved the pain symptoms (MD = −17.00; 95% CI: −21.41 to −12.58; p < 0.00001), joint stiffness (MD 3.43; 95% CI: −5.50 to −1.37; p = 0.001), and joint function (MD = 33.45; 95% CI: 48.74 to 18.17; p < 0.0001). Wu Qin Xi can also decrease pain, as VAS scores revealed an improvement (MD 1.07; 95% CI: −1.97 to −0.17; p = 0.02).
Yoga	Lauche et al. [66]	9 (n = 640; B)	The studies revealed effects of yoga on pain (vs. exercise, SMD = −1.07; 95% CI: −1.92 to −0.21; p = 0.01; vs. non-exercise, SMD = −0.75; 95% CI: −1.18 to −0.31; p < 0.001), physical function (vs. exercise, SMD = 0.80; 95% CI: 0.36 to 1.24; p < 0.001; vs. non-exercise, SMD = 0.60; 95% CI: 0.30 to 0.98; p < 0.001), and stiffness (vs. exercise, SMD = −0.92; 95% CI: −1.69 to −0.14; p = 0.008; vs. non-exercise, SMD = −0.76; 95% CI −1.26 to −0.26; p = 0.003) in KOA individuals.

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Table 4 (continued)

Interventions	Authors (A to Z; year)	No of included RCTs (subjects; grade)	Results/Conclusions
Musculoskeletal manual manipulations			
	Anwer et al. [46]	11 (n = 494; B)	The results indicated a statistically insignificant reduction of VAS score with orthopaedic manual therapy compared with the control group was (SMD = −0.59; 95% CI: −1.54 to −0.36; p ¼ 0.224). However, there was a statistically signi ficant reduction in VAS score with orthopaedic manual therapy compared to exercise therapy (SMD = −0.78; 95% CI: −1.42 to −0.17; p = 0.013). There was a statistically signi ficant reduction in WOMAC pain (SMD = −0.79; 95% CI: −1.14 to −0.43; p = 0.001) and function (SMD = −0.85; 95% CI: −1.20 to −0.50; p = 0.001) with orthopaedic manual therapy compared to the exercise therapy group. However, the reduction in WOMAC global score with orthopaedic manual therapy compared to the exercise therapy group was statistically insigni ficant (SMD 0.23; 95% CI: 0.54 to 0.09; p = 0.164). A statistically signi ficant reduction was found in the time taken to ascend and descend stairs in the orthopaedic manual therapy group compared to the exercise therapy group (SMD 0.88; 95% CI: 1.48 to 0.29; p = 0.004).
	Runge et al. [83]	19 (n = 1394; B)	Therewas very low- tomoderate-certainty evidencethat manual therapy when addedtoexercise, provided benefit in the short-term for pain (SMD = −0.82; 95% CI: −1.22 to −0.43) and WOMAC global score (SMD = −1.05; 95% CI: −1.52 to −0.59), but not for TUG (MD = −0.12; 95% CI: −0.27 to 0.03) and WOMAC function (SMD = −0.27; 95% CI: −0.85 to 0.30). In the medium-term, there was low- to very-low-certainty evidence that MT added bene fit for TUG (MD = −2.20; 95% CI: −2.89 to −1.51) and WOMAC global score (MD = −7.40; 95% CI: −10.31 to −4.49), but not for pain (MD = −0.97; 95% CI: 2.02 to 0.09) and WOMAC physical function (MD = 0.23; 95% CI: 6.36 to 6.82). There was high-certainty evidence that manual therapy did not provided any additional bene fit in the long-term for pain (MD 0.14; 95% CI: 0.48 to 0.21), TUG (MD = 0.39; 95% CI: 0.30 to 1.08) and WOMAC global score (MD = 0.56; 95% CI: 8.45 to 9.57; p = 0.90).
	Weleslassie et al. [95]	15 (n = 704; B)	Theresultssuggestsththerewereresignificant differences between mobilization with movement groups and control groups in terms of VAS, WOMAC Index scale, and flexion ROM.
Needle-based therapies			
Acupuncture therapy	Gong et al. [57]	17 (n = 4774; B)	Acutherapy hada significant effect on knee pain (SMD 0.73; 95% CI: 0.98 to 0.47; p < 0.001), knee stiffness (SMD 0.66; 95% CI: 0.85 to 0.47; p < 0.001), and physical function (SMD 1.56; 95% CI: 2.17 to 0.95; p < 0.001) compared to a control condition without any acutherapy intervention. Additionally, acutherapy was found to be more effective than a corresponding sham intervention applied on nonacupoints (SMD 0.16; 95% CI: 0.32 to 0.01; p = 0.04). However, there were no signi ficant differences found in treatment effects between acutherapy and sham acutherapy at the same acupoints (SMD 0.09; 95% CI: 0.40 to 0.21; p = 0.55).
	Sun et al. [86]	8 (n =2106; B)	Compared with low- and medium-dosageacupuncturetreatments, strongevidenceshowed that there was a positive correlation between high-dosage acupuncture treatment and positive outcomes.
Dry needling	Jim énez-del-Barrio et al. [64]	7 (n = 291; A)	Intheshort-term,dryneedlingdemonstratedsignificant improvements in pain intensity (SMD 0.76; 95% CI: 1.24 to 0.29; p =0.002) and physical function (SMD 0.98; 95% CI: 1.54 to 0.42; p = 0.0006). However, no signi ficant differences were observed in the medium- or long-term.
	Ughreja and Prem [92]	9 (n = 779; A)	Subgroupanalysisof moderate-quality evidenceshowsthatperiosteal stimulationtechniquehasshort-term effects on pain (post-treatment, MD = −1.13; 95% CI: −1.31 to −0.95; p < 0.00001; 3-month follow-up, MD = −1.46; 95% CI: −2.43 to −0.50; p = 0.003) and WOMAC function (post-treatment, MD = −5.47; 95% CI: −7.56 to −3.37; p < 0.00001; 3-month follow-up, MD = −4.95; 95% CI: −9.69 to −0.21; p = 0.04). Intramuscular electrical stimulation has a signi ficant effect on pain (MD = −2.30; 95% CI: 4.4 to 0.20; p = 0.03) in KOA. The myofascial trigger point needling technique showed signi ficant within-group differences in pain and knee function, but no signi ficant differences were found between the dry needling and sham dry needling groups. A meta-analysis was not performed for this technique due to the lack of studies that could be compared.
Nutrition therapies			
Diet therapy	Chu et al. [52]	7 (n = 1105; B)	Thestudyresultsindicatethatweightlosshadasignificant positive effect on pain (SMD = 0.33; 95% CI: 0.17 to 0.48; p < 0.0001), self-reported disability (SMD = 0.42; 95% CI: 0.25 to 0.59; p < 0.00001), QOL (physical) (SMD = 0.39; 95% CI: 0.24 to 0.54; p < 0.00001), WOMAC index (SMD =0.37; 95% CI: 0.11 to 0.62; p = 0.004), and 6-MWT (SMD = 0.23; 95% CI: 0.06 to 0.40; p = 0.009). However, no signi ficant improvements were observed in the timed stair climb test (p = 0.20).

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Table 4 (continued)

Interventions	Authors (A to Z; year)	No of included RCTs (subjects; grade)	Results/Conclusions
	Hall et al. [60]	16 (n = 2142; A)	The study found that diet-only treatments did not result in a reduction of pain (SMD = .0.13; 95% CI: 0.37 to 0.10; p = 0.10). However, a combination of diet and exercise treatments did moderately reduce pain (SMD = −0.37; 95% CI: −0.69 to −0.04; p ¼ 0.112). Physical function showed moderate improvement with both diet treatments (SMD 0.30; 95% CI: −0.52 to −0.08; p = 0.08) and 0.32; 95% combined diet and exercise treatments (SMD CI: 0.56 to −0.08; p =−0.265). Of all the inflammatory markers that were assessed, only interleukin-6 showed a reduction with diet-only treatments (SMD 0.23; 95% CI: 0.45 to 0.02; p = 0.38).
Dietary supplements	Liao et al. [71]	6 (n = 242; B)	The group that received protein supplementation combined with exercise training showed significant improvements in muscle mass (SMD= 1.13; 95% CI: 0.72 to 1.53; p < 0.00001), pain (SMD= 1.36; 95%CI: 0.68 to 2.03; p < 0.00001), and muscle strength (involved leg, SMD = 0.44; 95% CI: 0.03 to 0.85; p = 0.04; uninvolved leg, SMD = 0.54; 95% CI: 0.13 to 0.95; p = 0.01).
Patient education			
	Goff et al. [56]	29 (n = 4107; A)	Patienteducation wasfoundtobemoreeffectivethanusual careinimprovingpain(SMD = 20.35; 95%CI: 20.56 to 20.14) and function in the short-term (SMD = 20.31; 95% CI: 20.62 to 0.00). However, it was less effective than exercise therapy in reducing pain in the short-term (SMD = 0.77; 95% CI: 0.07 to 1.47). Combining patient education with exercise therapy resulted in better outcomes for pain in the short-term (SMD =0.44; 95% CI: 0.19 to 0.69) and function in the short- (SMD= 0.81; 95% CI: 0.54 to 1.08) and medium-term (SMD = 0.39; 95% CI: 0.15 to 0.62). When comparing results using the WOMAC Index, it was found that exercise therapy was more effective than patient education for short-term pain relief (MD = 1.56; 95% CI: 0.14 to 2.98). Additionally, a combination of patient education and exercise therapy was found to be more effective than patient education alone for short-term improvement in function (MD = 8.94; 95% CI: 6.05 to 11.82).
	Safari et al. [84]	8 (n = 2687; B)	Studies reported that digital-based structured self-management programs compared with the treatment as usual control group resulted in a signi ficant medium reduction in pain (SMD 0.28; 95% CI: 0.38 to 0.18) and improvement in physical function (SMD 0.26; 95% CI: 0.35 to 0.16) at post-treatment. Although the effect of digital-based structured self-management programs on pain and function reduced slightly at the 12-month follow-up, it remained medium and signi ficant. The effect of digital-based structured self-management programs after treatment was small and significant for disability (SMD 0.10; 95% CI: 0.17 to 0.03), but not signi ficant for QOL (SMD 0.17; 95% CI: 0.47 to 0.14). The intervention's effect at the 12-month follow-up was very small for both disability and QOL.
	Uritani et al. [93]	7 (n = 1123; B)	Group-based and face-to-face self-management education programmes have been found to have beneficial effects on self-ef ficacy for managing pain and other symptoms, as well as for self-regulating KOA. However, due to the wide range of clinical heterogeneity, most of the information in the systematic review was inconclusive.
	Wu et al. [98]	13 (n = 1610; B)	Meta-analysis revealed significant differences between the self-management and control groups in pain (SMD 1.51; 95% CI: 2.41 to 0.62; p = 0.001), function (SMD 0.24; 95% CI: 0.45 to 0.04; p = 0.02), arthritis self-ef ficacy (pain, MD = 2.82; 95% CI: 0.35 to 5.29; p = 0.03; other symptoms, SMD = 3.99; 95% CI: 1.55 to 6.43; p = 0.001), and mental health (MD = 3.82; 95% CI: 3.31 to 4.32; p < 0.00001). However, no statistically signi ficant differences were found in the WOMAC index.
	Xie et al. [99]	6 (n = 791; B)	Thestudy found that internet-basedrehabilitation programs can significantly reduce osteoarthritic pain in patients compared to conventional rehabilitation (SMD 0.21; 95% CI: 0.4 to 0.01; p = 0.04). However, there was no signi ficant difference in physical function improvement between patients with KOA who underwent internet-based rehabilitation and those who underwent conventional rehabilitation within 2 −12 months (SMD 0.08; 95% CI; 0.27 to 0.12; p = 0.43).
Physical agents			
Cryotherapy	Dantas et al. [53]	5 (n = 202; B)	Low-quality evidence showed improvements in pain control and functional outcomes.
Electric stimulation therapy	Chen et al. [49]	10 (n = 493; B)	The groups that received interferential current therapy showed significant improvements in short-term pain scores (SMD 0.64; 95% CI: 1.04 to 0.25; p = 0.001), long-term pain scores (SMD 0.36; 95% CI: 0.60 to 0.11; p = 0.005), and short-term WOMAC index scores (SMD 0.39; 95% CI: 0.77 to 0.02; p = 0.04) compared to the control groups.
Extracorporeal shockwave therapy	Avendano-Coy et al. [47]	14 (n = 782; A)	Extracorporeal shockwavetherapy causedadecreaseonthepainVAS(MD¼ 1.7; 95% CI: 1.1 to 2.3) and WOMAC (MD= 13.9; 95%CI: 6.9 to 20.8). The effect of extracorporeal shockwave therapy using medium energetic density was greater than with low or high density in the WOMAC (X^2 = 9.8; p =0.002) and bordered statistical signi ficance on the VAS (X^2 = 3.8; p = 0.05). Extracorporeal shockwave therapy causes moderate improvement in the knee ROM (MD = 17.5; 95% CI: 9.4 to 25.5) and walking test (SMD = 0.58; 95% CI: 0.35 to 0.81).

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Table 4 (continued)

Interventions	Authors (A to Z; year)	No of included RCTs (subjects; grade)	Results/Conclusions
	Chen et al. [51]	32 (n = 2408; B)	Extracorporeal shockwave therapy demonstrated significant improvement in pain reduction and functional improvement compared to placebo, corticosteroid, hyaluronic acid, medication, and ultrasound ($p < 0.05$). In terms offunctional improvement, shockwave therapy showed statistically significant improvement compared to kinesiotherapy and moxibustion ($p < 0.05$), but not with acupotomy surgery ($p = 0.24$). A statistically signi ficant difference was observed in pain reduction ($p < 0.05$) between shockwave therapy and platelet-rich plasma, but not in functional improvement ($p = 0.89$). Similarly, a statistical difference was found in functional improvement ($p < 0.05$) between extracorporeal shockwave therapy and fumigation, but not in pain reduction ($p ¼ 0.26$). Furthermore, there was no statistically signi ficant difference between extracorporeal shockwave therapy and manipulation in both pain reduction ($p = 0.21$) and functional improvement ($p = 0.45$).
	Li et al. [67]	7 (n = 366; B)	Theextracorporeal shockwavetherapy groupexhibiteda lower VAS score(MD 2.35; 95% CI: 2.92 to 1.79; $p < 0.00001$), larger ROM (MD = 17.58; 95% CI: 12.88 to 22.28; $p < 0.00001$) and a better Lequesne index (MD 3.06; 95% CI: 3.90 to 2.21; $p < 0.00001$) than the placebo group after 1 month of therapy. At 1 month post-therapy, the group that received extracorporeal shockwave therapy had a lower VAS score (MD 1.98; 95% CI: 2.93 to 1.03; $p < 0.00001$), a larger ROM (MD= 11.69; 95% CI: 6.40 to 16.98; $p < 0.00001$), and better WOMAC scores (MD 15.38; 95% CI: 18.87 to −11.89; $p < 0.00001$) compared to the group that received physical therapy.
	Liao et al. [70]	50 (n = 4844; B)	Resultsindicateasignificant improvement in the success rate of shockwave therapy (OR = 3.22; 95% CI: 2.21 to 4.69; $p < 0.00001$), pain reduction (SMD = −2.02; 95% CI: −2.38 to −1.67; $p < 0.00001$), and WOMAC Index function outcome (SMD = −2.71; 95% CI: −3.50 to −1.92; $p < 0.00001$).
Laser therapy	Ahmad et al. [43]	10 (n = 495; B)	Statistically significant improvements were observed in the VAS (SMD = −0.67; 95% CI: −1.05 to −0.29; $p < 0.05$) and WOMAC function (SMD = −0.70; 95% CI: −1.36 to −0.04; $p < 0.05$) scores of patients treated with low-level laser therapy plus exercise compared to the control group. However, no significant difference was found between the two groups in the WOMAC pain and stiffness scores. High-level laser therapy was found to be superior to the control group in terms of VAS (SMD = −2.06; 95% CI: −3.14 to −0.98; $p < 0.05$), WOMAC pain (SMD = −2.03; 95% CI: −3.81 to −0.26; $p = 0.02$), stiffness (SMD = −0.84; 95% CI: −1.43 to −0.24, $p < 0.05$), and function (SMD = −3.11; 95% CI: −5.59 to 0.62; $p < 0.05$) when compared to the control group.
	Stausholm et al. [85]	22 (n = 1063; B)	Overall, low-level laser therapy significantly reduced VAS compared to placebo at the end of therapy (MD = 14.23; 95% CI: 7.31 to 21.14; $p < 0.0001$) and during follow-ups 1 –12 weeks later (MD = 15.92; 95% CI: 6.47 to 25.37; $p = 0.001$). The results of the subgroup analysis indicate that the recommended low-level laser therapy doses signi ficantly reduced pain compared to placebo at the end of therapy (MD = 18.71; 95% CI: 9.42 to 27.99; $p < 0.0001$) and during follow-ups 1 –12 weeks after the end of therapy (MD = 23.23; 95% CI: 10.60 to 35.86; $p = 0.0003$). The greatest reduction in pain from the recommended low-level laser therapy doses was observed during follow-ups 2 –4 weeks after the end of therapy (MD = 31.87; 95% CI: 18.18 to 45.56; p 0.01). Low-level laser therapy signi ficantly reduced disability compared to placebo at the end of therapy (MD = 0.59; 95% CI: 0.33 to 0.86; $p < 0.00001$) and during follow-ups 1 –12 weeks later (MD = 0.66; 95% CI: 0.23 to 1.09; $p = 0.003$). The subgroup analysis showed that the recommended low-level laser therapy doses signi ficantly increased disability compared to placebo at the end of therapy (MD = 0.75; 95% CI: 0.46 to 1.03; $p < 0.00001$) and during follow-ups 1–12 weeks after the end of therapy (MD= 1.31; 95% CI: 0.92 to 1.69; $p < 0.00001$).
	Wu et al. [97]	10 (n = 580; B)	High-intensity laser demonstratedthehighestprobability of beingamongthemosteffectivetreatments, compared to a control (placebo laser, exercise, or a combination of both) in the VAS (WMD = 1.66; 95% CI: 1.48 to 1.84; $p < 0.00001$) and WOMAC (WMD = 10.87; 95% CI: 8.85 to 12.88; $p < 0.00001$). Comparing low- to high-intensity laser, differences were found in WOMAC (WMD = 6.48; 95% CI: 4.07 to 8.89; $p < 0.00001$) and pain (WMD = 0.81; 95% CI: 0.44 to 1.18; $p < 0.00001$), favoring high-intensity laser.
Magnetic field therapy	Chen et al. [50]	8 (n = 421; B)	Pulsed electromagnetic field therapy improved physical function (WMD = −5.28; 95% CI: −9.45 to −1.11, $p = 0.01$), but did not show advantage in reducing WOMAC total score (WMD = −7.80; 95% CI: −16.08 to 0.47; $p = 0.06$), WOMAC pain score (WMD = −1.06; 95% CI −2.30 to 0.17, $p = 0.09$), VAS pain score (WMD = −0.88; 95% CI: −2.06 to 0.31, $p = 0.15$), or WOMAC stiffness score (WMD = −0.50; 95% CI: −1.09 to 0.09; $p = 0.1$).
	Tong et al. [89]	11 (n = 614; B)	Compared to the control groups, pulsed electromagnetic field therapy yielded more favorable results. It alleviated pain (SMD = 0.71; 95% CI: 0.08 to 1.34; $p = 0.03$), improved stiffness (SMD = 1.34; 95% CI: 0.45 to 2.23; $p = 0.003$), and restored physical function (SMD = 1.52; 95% CI: 0.49 to 2.55; $p = 0.004$).

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Table 4 (continued)

Interventions	Authors (A to Z; year)	No of included RCTs (subjects; grade)	Results/Conclusions
	Yang et al. [100]	16 (n = 1078; B)	Comparedtotheplacebogroup, electromagnetic field therapy was found to have a bene ficial effect on pain (SMD = 1.06; 95% CI = 0.61 to 1.51; p < 0.00001), stiffness (SMD = 0.37; 95% CI: 0.07 to 0.67; p = 0.02), and function (SMD = 0.46; 95% CI: 0.14 to 0.78; p = 0.005). However, no statistically significant differences were found for QOL (SMD = 1.49; 95% CI: 0.06 to 3.04; p = 0.06). Electromagnetic field therapy parameters, such as duration of treatment, may not be a critical factor to influence symptoms.
Ultrasonic therapy	Chen et al. [48]	13 (n = 807; B)	Low-intensity pulsed ultrasound significantly improved the VAS (MD = −0.95, 95% CI: −1.43 to −0.48; p < 0.001), WOMAC index score (MD = −4.35; 95% CI: −8.30 to −0.40; p = 0.0309), Lysholm score (SMD = 1.59; 95% CI: 1.29 to 1.90; p < 0.001), Lequesne index (MD = −1.33; 95% CI: −1.69 to −0.96; p< 0.001), ROM (MD = 2.43; 95% CI: 0.39 to 4.46; p = 0.0197) and 50-m walking time (SMD = 1.48; 95% CI: 0.46 to 2.49; p = 0.0044). Subgroup analyses revealed that low-intensity pulsed ultrasound monotherapy was more effective in reducing VAS (p= 0.0213), while a shorter therapeutic period (4 weeks) was more effective in increasing the WOMAC score (p = 0.0083).
	Dantas et al. [54]	5 (n = 234; B)	Therapeutic ultrasonic therapy resulted in statistically significant pain relief (SMD = −0.33; 95% CI: −0.60 to −0.07; p = 0.01) and improved self-reported function (SMD = −0.33; 95% CI: −0.65 to −0.01; p= 0.05) compared to sham treatment.
	Liu et al. [73]	14 (n = 1080; B)	Bothpulsed(SMD= 1.11; 95% CI: 0.86 to 1.36; p < 0.00001) and continuous ultrasound (SMD = 1.18; 95% CI: 0.78 to 1.57; p < 0.00001) therapy were found to have signi ficant pain relief effects. High-intensity ultrasound (> 1.5 W/cm ^{2}) appeared to be more effective than other intensities (SMD = 1.34; 95% CI: 0.94 to 1.73; p < 0.00001). Additionally, therapeutic ultrasound was effective in improving joint function as measured by WOMAC (SMD = 8.18; 95% CI: 5.88 to 10.48; p < 0.00001).

Abbreviations : 6-MWT, 6-min Walk Test; KOA, knee osteoarthritis; MD, mean difference; NSAID, non-steroidal anti-in flammatory drug; OR, odds ratio; QOL, quality oflife; ROM, range of motion; SF-36, Short Form Health Survey 36-item; SMD, standardized mean difference; TUG, Timed Up and Go test; VAS, Visual Analogic Scale; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Universities Arthritis.

KOA patients. Moreover, there are indications of long-term enhancements in overall QOL (including social functions), in comparison with sham mud/peloid therapy, or standard treatment. Similarly, it was also found that balneological interventions in adjunct to standard treatment are significantly more effective than standard treatment alone in improving QOL. Interestingly, social function does not seem to be directly influenced by the treatment itself. This could be attributed to the fact that, regardless of the type of intervention (real or sham), patients were asked for a short period to regularly go to a spa center, where they could relax, socialize with other people, and carefully assessed by physicians. Both real and sham balneological interventions may contribute to an improved self-perception of well-being and social function, possibly due to placebo effects (primarily attributed to the ritualistic nature of the intervention, the therapeutic environment, and the patient-clinician relationship dynamics). Due to wide range of interventions included in the umbrella term "balneology", moderate risk of bias, and publication bias found, these interventions are considered a B.

4.3. Aquatic therapy

From the reviews [55,76], Ma et al. [76] found that compared with no aquatic physical therapy, aquatic physical therapy is associated with a large significant change in pain. Furthermore, for muscle strength, aquatic physical therapies exhibit a small but significant effect on knee extension muscle strength. Mixed results were achieved in physical function and walking ability (although the overall results show a tendency of improvement). Conversely, aquatic physical therapy did not significantly relieve knee stiffness and symptoms, QOL, ROM, and body composition. Dong et al. [55] found that compared to no intervention, the aquatic group had significant enhancements in KOOS activities of daily living and sports & recreational activities, but not for KOOS pain, symptom, or QOL. Despite a higher level of adherence and satisfaction reported in the aquatic therapy group, it did not outperform land-based therapy in all evaluated outcomes.

These mixed results can be attributed to the heterogeneity among the methodologies employed in the individual studies, particularly regarding exercise prescription parameters (such as mode, intensity, duration and frequency, and water characteristics) [55,76]. The studies had sessions typically ranged 40–60 min, conducted 2–3 times per week over a span of 6–18 weeks, with water depths ranging 1.15–1.5 m and temperatures between 30 and 34 C [55]. These methodological discrepancies likely influenced the obtained results. For instance, due to water resistance and buoyancy, the aquatic exercise program intensity is quite different to land-based [55], therefore these different groups may achieve the same effects under different intensities. Moreover, water properties such as temperature and depth play crucial roles in these interventions. A temperature range 33.5–35.5 C is best suitable as it allows lengthy immersion and thus enables sufficient exercise to be performed to achieve therapeutic effects without participants becoming cold or over-heating, and may promote muscle relaxation [55,76]. Additionally, varying water depths (xiphoid or cervical) can lead to distinct buoyancy effects, impacting joint load-bearing and influencing outcomes such as pain alleviation, stiffness reduction, strength enhancement, and improvement in physical function [55,76]. Considering the aforementioned factors, these interventions are categorized as B.

4.4. Balance training

The reviews [80,94] suggests that compared to no intervention, balance/ proprioceptive training group was superior across all outcome measures. However, when compared to other training methods, the results are less elusive, with differences observed simply in joint position sense, knee ROM, and physical function. Notably, the addition of balance/ proprioceptive training to other interventions (such as conventional physiotherapy or other exercise regimens), resulted in sustained superiority solely in joint position sense. Consequently, it is prudent to consider this intervention as a complementary component to standard exercise or physiotherapy protocols, particularly recommended for patients displaying significant clinical impairments in joint position sense. It should not be regarded as an individual intervention. Considering the low publication bias and the very-low to moderate-quality of evidence, these interventions are classified as B (when utilized as a complementary exercise).

Key points

- **Balneology:** Mud therapy enhances overall quality of life and social functions compared to sham treatments or standard care, with some potential placebo effects. Rated as moderate quality (B).
- **Aquatic Therapy:** Significantly reduces pain and improves knee strength, though results for physical function are mixed. Methodological variations affect outcomes. Classified as moderate quality (B).
- **Balance Training:** Shows superior results over no intervention, particularly in joint position sense. Should be a complement to other therapies, rated as moderate quality (B).

Key points

- **Blood Flow Restriction (BFR) Training:** Effective for pain and strength in KOA but low quality due to inconsistent results and safety concerns.
- **Circuit-Based Exercise:** Improves pain and quality of life but shows limited effectiveness in other outcomes.
- **Resistance Training:** Cost-effective with significant improvements in pain and strength, outperforming traditional pain management.
- **Methodological Variability:** Standardized approaches are needed for non-pharmacological KOA interventions to enhance evidence quality.

4.5. Blood flow restriction therapy (BFR)

Based on the reviews [58,81], it appears that this intervention can reduce pain and improve strength. However, it failed to surpass standard resistance training [58] or high-intensity training [81] regimens. Nonetheless, despite the limited number of studies, a guidance is starting to emerge. Although the precise mechanism of action of this less explored intervention in the KOA context remains unclear, several theories have been proposed. BFR involves performing low-intensity exercises while applying cuffs in the upper third of the thigh, reducing arterial inflow and causing venous occlusion, leading to transient ischemia to the afferent tissues [104–106]. It is hypothesized that this technique will potentially stimulate neovascularization and promote various biochemical and physiological tissue changes such as hypertrophy, increased fast-twitch fiber recruitment, mechanotransduction, muscle damage, systemic and localized hormone production, cell swelling, and the production of reactive oxygen species and its variants (including nitric oxide and heat shock proteins) [107]. Consequently, this intervention appears to have the potential to be applied to KOA patients who require strength improvements and experience pain during exercises, particularly in more intense training regimens [58,81]. In terms of protocol variables, it should be performed at least six weeks, with a session frequency of 2–3 times weekly, with until voluntary failure volume, a rest period of 30–60 s, and a cuff pressure individualized and maintained throughout the session (40–80% of the arterial occlusion pressure more usual) [81]. While this intervention appears relatively safe, awareness among KOA patients with comorbid conditions (specially, cardiovascular [e.g., hypertension or chronic venous insufficiency]) is crucial, due to the potential effect on the exercise pressor reflex (a body's physiologic autonomic sympathetic response to exercise, that increases carbon monoxide, heart rate, contractility, and ultimately mean arterial pressure) [108,109]. Due to pain reporting inconsistencies, disparities in the protocols, inaccuracies in the one-repetition maximum calculation, limited studies, inefficacy compared to more traditional and established training regimens, and overall quality of evidence, this intervention is considered D.

4.6. Circuit-based exercise

Circuit-based training involves repeatedly and sequentially performing sets of several resistance and callisthenic exercises, targeting different body parts, with minimal or no rest intervals [110,111]. By its nature, the heart rate maintains raised throughout the workout and different muscle groups are activated, leading to a high metabolic cost [111]. Thereby, it is expected that it could promote both local (muscle/strength) and systemic (cardiorespiratory/functional capacity/body composition) benefits [110,111]. The brisk transition between exercises, coupled with shorter rest intervals, significantly reduces the session duration, which may encourage participant retention and adherence [110,112]. A recommendation for the elderly population is to engage a minimum of two weekly sessions, lasting 30–50 min (the sets and repetitions per exercise should be scalable by the individual training/fitness level and the clinical status), incorporating different intensity levels (hypertrophy [e.g., 60–85% 1 RM] and high-velocity low-loads [e.g., 40% 1 RM]), with a 1:1 work-to-rest ratio (e.g., 30:30 s) [110]. Despite the anticipated positive effects of this intervention, in the KOA population it fails to demonstrate is effectiveness. In fact, among all outcomes evaluated, circuit-based exercises solely exhibited improvements in the pain, depression, and health-related QOL compared to standard treatment groups [44]. In the other outcomes, no statistically significant differences observed between the groups [44]. Therefore, and due to the limited number of trials, inconsistencies among protocols, heterogeneity found in positive outcomes, and the overall quality of evidence, this intervention is classified as C.

4.7. Resistance training

Similar to findings in other studies [11,113,114], resistance training showed to be a cost-effective intervention for KOA patients. From the reviews [65,69,78,87,88,91], positive results were found in the overall explored outcomes (especially, pain, strength, QOL, function, and knee health-related status). These benefits were particularly evident when compared to non-exercise groups as opposed to other exercise regimens [65]. For example, the exercise group demonstrated superiority over NSAIDs and opioids groups in pain reduction [88]. Additionally, significant increases in lean mass, muscle thickness, and cross-sectional area

were observed in the exercise groups compared to non-exercise controls [69]. While most of the studies targeted in strengthening the quadriceps femoris, a holistic approach involving hip-focused exercises (e.g., abductors) is also recommended, as evidence suggests it can improve knee-symptoms [78,87]. Although it was found that 24 total sessions over an 8–12 week period produces large effect sizes, the optimal protocol for resistance training in KOA patients remains undetermined (although, the most common regimens prescribed are 2–3 sets, 8–12 repetitions, starting at a resistance maximum of 50–60% 1 RM, 3 times per week) [91]. Due to the consistency of positive results, and overall low risk of bias, this intervention is A classified.

4.8. Whole-body vibration (WBV)

From the review [82], it was found that this intervention (both lowand high-frequency) when combined with strengthening exercises could improve pain, physical function, and knee extensor strength, compared to a control group performing strengthening exercises alone. However, no significant improvement were found in stiffness, balance, QOL, and knee flexor strength. These results can be explained by the device mechanism of action. WBV involves standing, sitting, or lying on an oscillating platform, that generates vertical or lateral vibrations, at a pre-determined frequency [115]. These vibrations are transferred to the body, in which is thought that can stimulate muscle spindles, influencing the central mechanism and activating the alpha-motor neurons, subsequently triggering the vibration tonic reflex, which may contribute to modulating neuromuscular adaptations [116]. Therefore, is expected that it can improve muscle strength and decrease pain [117]. Nevertheless, current evidence regarding the physiological mechanisms, therapeutic effects, device parameters and usage on KOA remains controversial [82,117]. By these uncertainties, evidence quality, limited studies, and conflicting results, this intervention is classified as C.

4.9. Baduanjin

Baduanjin, a form of Qigong, is an ancient Chinese mind-body therapy that integrates spirit and meditation with slow and gentle postures, musculoskeletal stretching, and deep breathing [118]. Baduanjin exercise involves eight separate postures (support the heaven, draw a bow, hold up the hand, looking back, shake the hand and wag the tail, touch the feet, climbing and relax the back) that may have beneficial body effects, such as muscular strength, weight reduction, and physical, psychosocial, cognitive and spiritual well-being [119]. This intervention has fewer physical and cognitive demands compared to practices (like Tai Ji), making it suitable for the elderly beginner with KOA to practice in a short-time [120]. In fact, findings from the included review [103] suggest that Baduanjin exercise is superior in WOMAC scores when compared with non-exercise groups (such as, waiting list or patient education). When combined with NSAIDS, it not only maintained superiority in WOMAC but also demonstrated a higher pain decrease when compared with NSAIDs alone. However, the therapeutic efficacy of Baduanjin exercise relative to other exercises, interventions, or mind-body therapies remains uncertain. Given these uncertainties, along with the overall weak evidence, limited study availability, and some safety concerns (such as mild muscle pain, falls, and exercise-related injuries during sessions), this intervention is categorized as D.

4.10. Tai Ji

Tai Ji, a traditional Chinese martial art, involves low-intensity exercises characterized by flowing circular, gentle, graceful movements, which requires practitioners to concentrate on exercise and eliminate distractions, while consciously deep breath and relax joints/muscles to the maximum extent possible, attempting to maintain proper posture when weight shifting, thereby emphasizing balance and coordination of the mind and body [121,122]. Presently, there are various training styles, such as Chen, Yang, Wu Hao, Wu, and Sun [121]. Additionally, to meet contemporary needs, adaptations of traditional forms have emerged, such as the 24-form Tai Ji [122]. Tai Ji is considered a suitable exercise for the elderly due to its potential effects for both physical and mental well-being. By practicing Tai Ji exercise, it is expect maintenance or improvement in pain levels, cardiorespiratory capacity, body weight, balance, muscle strength, and ROM, without exacerbating arthritis symptoms [123]. Additionally, by Tai Ji simplicity, safeness, and meditative nature, it is expected that facilitate the reduction of learning failure frustration, fear of

Key points

- **Resistance Training:** Effective for KOA patients, focusing on both quadriceps and hip exercises, with a common regimen of 2–3 sets at 50–60% 1 RM. Classified as A due to consistent positive results and low bias.
- **Whole-Body Vibration (WBV):** Combined with strength exercises, WBV improves pain and knee strength but shows no significant effects on stiffness or quality of life. Evidence quality is low, leading to a classification of C.
- **Baduanjin:** This gentle Qigong practice demonstrates improved knee symptoms compared to non-exercise groups but lacks robust evidence and has safety concerns. It is categorized as D.
- **Tai Ji:** A traditional exercise with potential benefits for balance and pain management in KOA patients, but evidence quality is variable, necessitating further research.

Key points

- **Wu Qin Xi (WQX):** An easy-to-learn Qigong exercise with minimal knee flexion, showing improvements in pain and WOMAC scores. Classified as C due to limited evidence.
- **Yoga:** Combines physical postures and meditation, effective for pain and function in KOA patients but with low evidence quality. Classified as C.
- **Musculoskeletal Manual Manipulations:** Includes techniques like massage, aiming to relieve pain and improve function, but effectiveness in KOA needs more research.
- **General Insight:** WQX and yoga are promising for managing KOA symptoms, but further studies are needed to confirm their benefits.

falling, depression, and anxiety, among the elderly [124,125]. The findings of the included reviews [63,102] support these statements, as it was found significant improvements in pain, physical function, walking, balance, self-reported knee-related health status, and QOL (physiological and psychological), among Tai Ji groups compared with the control groups (especially no active interventions, such as no-exercise, standard care, waiting list, or education). Although it was not found a specific protocol or style that stood out, the majority of the studies prescribed a regimen consisting of sessions lasting 40–60 min each, conducted 2–3 times per week, over a period of 8–24 weeks. Considering the quality of evidence and the inconsistencies found in the studies, this intervention in considered B.

4.11. Wu Qin Xi (WQX)

WQX, a type of Qigong that mimics animal movements, is an ancient Chinese mind-body therapy [126]. Each routine contains two symmetrically movements and synchronized with controlled breathing, featuring the following movements [126,127]: tiger standing up and lunging forward to eat; deer holding its horns and running; bear shaking its arms and swaying its body; ape lifting and picking things upwards; crane stretching and flying. While WQX exercises are less well-known both internationally and in China compared to other Qigong forms, they offer distinct advantages. From example, compared to the simplified version of Tai Ji, WQX is easier to learn because it only has 10-sets of movements [59]. Furthermore, Tai Ji contains movements with extreme knee flexion, which could be detrimental to the KOA patients where, in contrast, all movements in WQX have knee flexion no greater than 90 [59]. Similar to other Qigong forms, WQX exercises may offer a physiological benefits as, for example, the support and weight shift of the knee joint in a semi-squat position in the tiger and deer movements, and the dynamic flexion and extension of the knee in a single-leg support position in the bird movement, potentially leading to local (strength) and systemic (balance and cardiorespiratory) improvements [59,127]. Beyond physical conditioning, this intervention may also yield psychological benefits by restoring the balance of "Yin" and "Yang" (as known as "Qi") through specific breathing patterns coupled with the intentional movement, thereby alleviating mental tension, reducing psychological stress, and promoting mental health [127]. From the supposed benefits of these exercises, the review [59] only demonstrated improvements in WOMAC and pain. For the other outcomes, the clinical importance of WQX exercises remains uncertain. Due to the limited evidence, moderate risk of bias, and the low adverse effects associated with this intervention, it is classified as C.

4.12. Yoga

Yoga is a form of mind-body therapy originating in ancient India, and in the Western context constitutes a number of practices, including physical practices (postures, asanas), breath regulation techniques (pranayama), mental practices (meditation, mindfulness), and relaxation [128]. Yoga has become a popular intervention of achieving and maintaining well-being and health [129]. Yoga sequences include a variety of postures (e.g., Mountain, Downward-Facing Dog, Warrior, Tree, Child's, Cobra, Bridge, Seated Forward Bend, Triangle, and Corpse) to improve stiffness, joint function, ROM, and strength [130,131]. Beyond physical activity, yoga also often incorporates breathing/relaxation/meditation exercises, which serve to alleviate stress and pain by releasing muscle tension, countering muscle tightness, and enhancing mental equilibrium [132,133]. The included review [66] found that compared to exercise and non-exercise groups, yoga appears be safe and beneficial in terms of pain intensity, physical function, and stiffness. However, no significant effects were observed concerning QOL or depression. It is important to note that these findings were derived from limited studies, with an overall very-low quality of evidence. Therefore, this intervention is classified as C.

4.13. Musculoskeletal manual manipulations

Musculoskeletal manual manipulations (commonly referred as Manual Therapy (MT)) can be defined as any hands-on therapy that may include soft issue techniques, moving joints in various and specific directions and at various speeds, or having the patient move the body part against the therapist's resistance [134]. Within this broad definition, several techniques are suitable such as massage, manual stretch, myofascial techniques, mobilizations, and manipulations [46,83,95]. They

can be utilized either individually or in combination during a session [25]. The choice of technique(s) is influenced by the clinical (e.g., experience), patient (e.g., personal characteristics, clinical status, and preferences) and external factors (e.g., session time) [135]. By applying these techniques, it is expected to Ref. [136]: improve tissues mobility and function; restore movement, stretching, or ROM; improve muscle activation and timing; decrease pain; and improve circulation. However, from the included reviews [46,83,95], some of these benefits were unclear. It was found that MT can be beneficial, when compared with non-active interventions, in the studied outcomes. Similarly, it was also found benefits when combined to an active intervention, however they were less evident. It was found benefits of combined MT and exercise over exercise alone for reducing pain (the larger effect), and improving function and WOMAC in the short- and medium-term. However, these findings were predominantly based on trials with very-low to moderate-level of certainty, thereby should be considered with caution. In long-term, high-certainty evidence showed that combined MT with exercise did not offer additional benefits compared to exercise alone in terms of pain, WOMAC, and function. Due to the polled results, the overall quality of evidence, the lack of protocol standardization (type, dosage, force, amplitude, rate, repetition, and duration), and the inclusion of several MT techniques under the same umbrella term, these interventions are categorized as C.

4.14. Acupuncture therapy

Acutherapy belongs to the Traditional Chinese Medicine, and is based on the principle of acupoint stimulation across meridians through a wide range of modalities, including needle acupuncture, laser acupuncture, acupressure, electroacupuncture, moxibustion, etc [57]. While evidence has been showing potential clinical benefits of acutherapy for KOA, controversy on its role in managing these patients remains [86]. Gong et al. [57] found that acutherapy presented benefits in pain, stiffness and function when compared with the usual care, but the differences were not significant as compared with the sham condition. The authors speculated that since differences existed between sham conditions (sham non-acupoints versus sham true-acupoints) the lack of differences found between sham and acutherapy could be attributed to potential therapeutic effects of sham true-acupoints. However, acutherapy did not demonstrate any apparent therapeutic advantages in pain, stiffness, and function over physiotherapeutic approaches, such as exercise-based interventions (e.g., exercise oriented leg strengthening, stretching, and balance). Consequently, the most plausible explanation for these outcomes is psychological factor dependent, potentially indicating a placebo effect. Another factor to consider is dosage. Sun et al. [86] showed that an adequate acutherapy dosage involved needling of 4 points (for each painful knee, for at least 20 min), 6 treatment sessions, conducted at least once weekly, with either elicitation of de qi sensation or application of electrical stimulation, and that high-dosages had more benefits compared to low- or medium-dosages. However, the criteria used to define high-dosage were as follows: (1) the number of points needled was 9; or (2) there was a de qi response; or (3) frequency of treatment was 2 sessions a week; or (4) the total number of treatment sessions was

8. These are volatile and unassertive, providing limited assistance in decision-making or clinical guidance. Therefore, and as explored, these inter-ventions are classified as C.

4.15. Dry needling (DN)

DN entails the insertion of fine monofilament needles through the skin to manage various neuromusculoskeletal syndromes [137,138]. These needles can target a variety of tissues, including muscles, subcutaneous fascia, tendons, ligaments, scar tissue, periosteum, teno-osseous junction, peripheral nerves, and even neurovascular bundles [137,138]. There are three primary DN techniques most common used [92]: myofascial trigger point needling, periosteal stimulation, and intramuscular electrical stimulation. Myofascial trigger point needling, is the most common invasive technique, and consists of repeated needle insertion of a single-use acupuncture needle into the trigger point (hyperirritable spot present in taut bands of skeletal muscles or fascia, which produce local and referred pain,

Key points

- **Musculoskeletal Manual Manipulations (MT):** Hands-on techniques may improve mobility and reduce pain, but results are inconsistent. Combined MT and exercise shows benefits; classified as C.
- **Acupuncture Therapy:** Offers potential pain relief but lacks significant advantages over sham treatments or physiotherapy. Due to variability in effectiveness, classified as C.
- **Dry Needling (DN):** Targets musculoskeletal tissues to alleviate pain. Effectiveness varies with technique; more evidence needed for conclusive results.
- **General Insight:** Both MT and acupuncture show potential but require standardized protocols and further evidence for effective clinical use.

Key points

- **Dry Needling (DN):** Provides mixed short-term benefits for pain relief and function in KOA patients, but inconsistent results classify it as D for clinical use.
- **Diet Therapy:** Effective in improving function and reducing weight in KOA patients, especially when combined with exercise. Classified as A when complementing exercise and B as a standalone treatment.
- **Dietary Supplements:** Protein supplementation enhances pain relief, muscle mass, and function in conjunction with resistance training. Due to variability in study protocols, it's classified as B when used alongside exercise.
- **Clinical Implication:** While promising, these interventions need standardized protocols and more robust evidence for definitive clinical recommendations.

stiffness, limited ROM, and muscle spasm, fatigue, and weakness) [137,138]. The periosteal stimulation employs a similar technique but uses needles over the periosteum [92]. The intramuscular electrical stimulation is another needling technique that uses electrical stimulation over motor points, regional, and paravertebral musculature [92]. With these techniques it is expected to reduce pain, relax muscles, and improve ROM, and activate circulation [137]. Nevertheless, the actual mechanisms are still elusive. Ughreja and Prem [92] found that periosteal stimulation could have booster short-term benefits in pain and WOMAC when added to conventional physiotherapy protocols. Intramuscular electrical stimulation, although less explored, demonstrated potential in reducing pain compared to sham intervention. However, caution is warranted in interpreting these findings, as the study yielding these results included an additional intervention in the form of active transcranial direct current stimulation, making it difficult to ascertain the individual effects of each intervention. Finally, the myofascial trigger point needling, was the most explored technique, and reached mixed results. While some studies reported differences in pain and function favoring DN over acupuncture, others found no changes between DN and sham interventions. Jimenez-del-Barrio et al. [64] also reported mixed results concerning this technique. Overall, DN demonstrated efficacy in reducing pain and improving function in the short-term compared to control groups, particularly when contrasted to sham or no intervention. However, when compared to more active interventions (such as, exercise or self-stretching), the results were less obvious. No differences in medium- or long-term were found. Therefore, due to the inconsistency of the results, the very-low to low-quality of evidence, and safety concerns (e.g., post-needling soreness), these interventions are categorized as D.

4.16. Diet therapy

Diet therapy is a form of intervention that adjusts the quantity and quality of food intake to improve health status of an individual. These interventions for KOA patients encompassed various approaches, including: nutritional education and behavioral therapy about reduced energy diets; partial meal replacements; and nutrition powder to fully replace conventional meals. While some improvements were noted with diet-only interventions (particularly function), more consistent results were observed when diet was combined with exercise (particularly pain). However, it is important not to underestimate the efficacy of these interventions as, for example, significant reductions in total weight and fat mass were observed in the diet groups compared to the control groups (8.5 2.9 kg [7.8 3.1 %] vs 2.7 1.3 kg [2.7 1.2 %]; and 7.6 1.0 kg [3.3 0.4 %] vs 2.1 1.4 kg [0.4 1.3 %], respectively) [52]. Additionally, it appears that these patients have more benefits when these interventions are sustained over longer durations (þ12 months), without encountering adverse effects during that time [60]. Consequently, these interventions are dual-classified as both A (as a complement to exercise) and B (as a standalone intervention).

4.17. Dietary supplements

Dietary supplements can be defined as products in capsule, tablet or liquid form that provide dietary ingredients, and that are intended to be taken by mouth to increase the intake of nutrients [139]. Dietary supplements can include macronutrients (such as proteins, carbohydrates, and fats) and/or micronutrients (such as vitamins, minerals, and phytochemicals) [139]. In this subsection, only protein supplements was explored [69]. The protein supplements administered consisted of either whey protein (milk or leucine) or branched-chain amino acids. The essential amino acid doses varied between 3 and 40 g/day, and were administered to a resistance training intervention group. It was found that, compared to groups receiving exercise plus placebo supplementation or exercise alone, the intervention group exhibited statistically significant improvements in pain, muscle mass, strength, and function outcomes. These results are particularly interesting, given that deficits in muscle volume and function are commonly observed in KOA patients, often attributed to the development of sarcopenia (a condition associated with gradual and progressive muscle mass loss in older adults), that frequently result in a poorer health status and QOL [140]. Due to the limited studies, and inconsistencies among protocols and doses, this intervention is classified as B (as a complement to exercise).

4.18. Patient education

Patient education interventions were scrutinized in five reviews [56, 84,93,98,99]. This intervention aims to teach or train patients regarding their own health-needs. Therefore, it may be used a range of modalities to achieve its objectives, including exercises guidance, diet or weight management, physical, psychological, and occupational therapies, cognitive or behavioral pain coping skills, as well as encouragement, medication, educational lectures, and medical information. The reviews revealed a short- and medium-term reduction in pain, and improvement in function among patients who received educational interventions, compared to those who received usual care or no intervention. Similarly (but superior), when educational interventions were combined with conventional rehabilitation, outcomes were enhanced compared to conventional rehabilitation alone. However, when compared to more active interventions (such as exercise), the improvements in outcomes were less pronounced. Long-term results were either non-existent or slightly/very small for the majority of the outcomes, regardless of the compared group. Intriguingly, therapist-based educational interventions (whether group or face-to-face) yielded consistently superior positive results compared to internet-based interventions. Therefore, to achieve more consistent results, it is recommended to adopt a more personal approach in these interventions. Consequently, these interventions are dual-classified as both A (as a complement to exercise) and C (as a standalone intervention).

4.19. Cryotherapy

Cryotherapy consists in the local or general use of cold encompassing various modalities, including ice packs, ice cubes, cold compresses, cold sprays, cold tubs, and cold chambers. From low-quality evidence [53], it was found high within-group effects sizes when cryotherapy was combined with other types of therapy (e.g., exercises or analgesics), in pain and function. Moreover, between-group comparisons yielded only small effect sizes. However, when cryotherapy was administered alone, the effect sizes were generally moderate for both within-group and between-group comparisons. Although study protocols varied, the techniques, frequency, and duration of cryotherapy applications did not significantly impact the outcomes. Furthermore, the results should be interpreted with caution, as the small sample sizes may increase the likelihood of encountering a type II error. For the reasons stated before, these interventions are classified as C.

4.20. Electric stimulation therapy

The review [49] that explored electric stimulation therapy focused solely on interferential current therapy (IFC). IFC is a type of electrical stimulation therapy, which involves the use of two or more sinusoidal currents (applied to the body via electrodes), intersecting and "interfering" with each other at the target area to generate a "beat frequency" and induce a therapeutic effect [141]. Findings indicated that this therapy could yield positive outcomes in short-term pain reduction and WOMAC scores compared to control groups. However, in the long-term, only pain reduction remained statistically significant. No statically significant differences were observed for mobility and stiffness. Results were more pronounced when active IFC was compared with sham IFC. Conversely, for other combinations and comparisons (e.g., active IFC plus exercise versus sham IFC plus exercise or exercise alone), outcomes were less evident. Although the studies applied more frequently a carrier frequency of 3850–4000 Hz and an amplitude modulated frequency 80–100 Hz, a consistent treatment protocol for IFC application was not established. Nonetheless, this lack of uniformity may not pose a significant issue, as research suggests that most IFC parameters do not appear to influence its analgesic effects [142]. Although previous studies have reported adverse effects (such as, burns and vasovagal reactions), no adverse effects of similar severity were reported in the selected studies. Therefore, these interventions are double-evaluated as B (as a complement to exercise) and C (as a standalone intervention).

4.21. Extracorporeal shockwave therapy

This therapy operates by generating shockwaves through electromagnetic means, involving the passage of electric current through a coil to produce a strong magnetic field [143]. The waves are then focused using a lens, precisely targeting the therapeutic focal point (determined by the lens length) [143]. As the acoustic wave advances towards the

Key points

- **Patient Education:** Effective in reducing pain and improving function, especially when combined with rehabilitation. Classified as A (complement to exercise) and C (standalone).
- **Cryotherapy:** Moderate benefits in pain relief when combined with other therapies, limited as a standalone. Classified as C due to low-quality evidence.
- **Electric Stimulation Therapy (IFC):** Provides short-term pain relief, with uncertain long-term effects. Classified as B (with exercise) and C (standalone).
- **Extracorporeal Shockwave Therapy:** Shows promise in pain reduction, but inconsistent results limit applicability. Classified as B (combined) and C (standalone).

Key points

- **Patient Education:** Enhances pain and function in KOA when combined with rehabilitation (A classification).
- **Cryotherapy:** Shows moderate benefits for pain and function when combined with other therapies (C classification).
- **Shockwave Therapy:** Effective for pain and ROM in KOA, especially with longer sessions and medium energy levels (B classification).
- **Laser Therapy:** High-level laser therapy is more effective than low-level, emphasizing the importance of treatment parameters (B and C classifications).

focal point, it initiates mechanotransduction, generating vibrations within tissues (energy that can develop a peak pressure about 1000 times higher than that of ultrasound), achieving its therapeutic effects [144]. Polled findings [47,51,67,70] indicate positive outcomes in pain reduction, ROM improvement, enhanced function, and self-reported knee-health status when compared to either placebo or other interventions. Most of these interventions consisted of 3–5 sessions, with 1000–2500 pulses per session, and a pulse frequency between 4 and 12 Hz. Certain parameters of extracorporeal shockwave therapy interventions merit special consideration, particularly follow-up duration, shockwave energy level, and type [47,67,70]. Results suggest that interventions lasting 4 weeks yield superior outcomes compared to <4 weeks [67,70]. Regarding the energetic density dosage, it seems that medium-doses (0.08–0.25 mJ/mm2 or 1.5–2.5 bar) produced a greater effects than low- or high-doses (<0.08 and >0.25 mJ/mm2 or <1.5 and >2.5 bar) [47]. Comparing low-to high-dosages, high-dosages produced better results than low [70]. Concerning the type of shockwaves, both focused and radial shockwaves are beneficial for KOA patients [47,51,67], although the radial shockwave may exert superior effects [70]. Due to overall quality evidence (moderate) and some safety issues found (e.g., pain, minor bruising, soft tissue swelling, redness, burning sensation, or effusion), this intervention is classified as B.

4.22. Laser therapy

Findings form the reviews [43,85,97] indicate that laser therapy is effective in reducing pain and improving WOMAC scores, particularly when compared to placebo or sham interventions. These benefits are further accentuated when laser therapy is combined with exercise [43]. Laser therapy encompasses both low- (LLLT) and high-level laser therapy (HLLT), and works by delivering specific wavelengths of light, that absorbed by the targeted tissues, triggering a cascade of biological responses [145]. LLLT and HLLT have different characteristics, with HLLT appearing to yield superior results for KOA patients compared to low-level [43,97]. Typically, LLLT involves longer continuous concentrated therapy time (e.g., 16 min), with 500 mW of energy output, 600–980 nm wavelength, 100 J/cm2 energy density, in 5 cm2 treatment area, having a potential penetration of <2 cm (superficial tissues) [43]. In contrast, HLLT features shorter continuous or pulsed diffuse therapy session (e.g., 2 min), with >500 mW of energy output, 660–1280 nm wavelength, 100 J/cm2 energy density, in 5 cm2 treatment area, having a potential penetration of 5–15 cm (deep tissues) [43]. The higher dosage delivered by HLLT effectively increase local temperature, thereby enhancing tissue metabolism and blood circulation [97]. This results in the rapid removal of inflammatory substances, improved mitochondrial oxidation and adenosine triphosphate production, enhanced absorption of tissue edema, and increased nutrient exchange and tissue regeneration [97]. Conversely, the local temperature increase is less pro-nounced with LLLT, potentially limiting its efficacy [85]. Despite variations in intervention procedures, studies suggest that the ideal protocol parameters include a wavelength of 1064 nm, an energy density of 15–810 J/cm2, a total dose per session of 1250–3000 J, 10–12 therapy sessions within a 2–6 week intervention period [43]. Consequently, this therapy is double-evaluated as B (HLLT as a complement to exercise) and C (LLLT as a complement to exercise, and laser therapy as a standalone intervention).

4.23. Magnetic field therapy

Pulsed electromagnetic field therapy (PEMF) utilizes a time-varying magnetic field generated by electrical current passing through a conductor, in which provides electrical stimulation piezoelectric scaffolds facilitating the transmission of mechanical impulses, potentially resulting in cellular proliferation, cartilage degeneration prevention, and subchondral trabecular bone microarchitecture stabilization [50,89, 100]. This therapy appears to offer potential improvements in pain, stiffness, and function when compared to placebo or sham groups [50,89, 100]. However, when contrasted with active controlled groups, these positive effects were less evidenced [89]. The most commonly applied protocol involves sessions lasting between 15 min and 2 h, occurring 3 times per week to daily (or twice daily), over a period of 4–6 weeks [50]. In terms of the therapy's parameters, it appears that low-frequency (i.e., <300 Hz) are more conducive to achieving favorable results when compared to high-frequency [89]. Other factors, such as duration of

treatment, may not be critical to influence KOA symptoms [100]. Due to the limited evidence, overall quality, and the modest results obtained, this intervention is classified with D.

4.24. Ultrasonic therapy (US)

US is a therapeutic modality that uses high-frequency sound waves to treat various medical conditions [146]. These sound waves penetrate into the body's tissues, creating thermal and mechanical effects [146]. With these effects is expected to enhance soft tissue healing, decrease the inflammatory response, increase blood flow, increase metabolic activity, decrease pain, and improve cartilage repair [146]. From the reviews [48, 54,73], it was found that this therapy could be effective in improving function, alleviating pain, enhancing ROM, and self-reported knee-health status, compared to either placebo or sham interventions. However, the comparison with other interventions yielded limited findings, precluding definitive conclusions. Regarding the US protocol parameters, evidence suggests that longer session durations (i.e.,≥20 min) over shorter periods (i.e.,≤4 weeks) tend to yield more favorable results [48]. Moreover, higher intensities (≥1.5 W/cm^2) are associated with tvqfsjps results dpnqbsfe to low-intensity treatments[73]. In terms of frequency, the US typically range from 0.2 to 3 MHz (1 MHz US is suitable for treating tissues with a 2.3–5 cm depth, and 3 MHz US is suitable for treating tissues with a 0.8–1.6 cm depth) [147]. The choice of frequency will depend on the desired therapeutic effect, though 1 MHz US appears more suitable for pain relief[73]. Unlike previous findings suggesting that pulsed modes are more effective, the included studies indicate no significant difference between pulsed and continuous modes[73]. Consequently, due to the limited outcomes achieved, the low-quality of evidence, and the minimal risk of adverse events associated, this intervention is classified as C.

5. Conclusion

Based in the systematic reviews included, it can be concluded that Diet Therapy, Patient Education, and Resistance Training are strongly supported as core interventions for managing KOA patients. Aquatic Therapy, Balance Training, Balneology, Dietary Supplements, Extracorporeal Shockwave Therapy, and Tai Ji show moderate support for their usage. However, for other interventions, the evidence quality was low, results were mixed or inconclusive, or there was not sufficient efficacy to support their use. Additionally, in comparison to Ferreira et al. [34], eleven new interventions were identified, including Baduanji, Balance Training, BFR, Circuit-based Exercise, Cryotherapy, Diet Therapy, Dietary Supplements, DN, Extracorporeal Shockwave Therapy, Patient Education, and WQX. In the contrary, no systematic reviews were included with the Cupping Therapy, Insoles, Moxibustion, Neuromuscular Electrical Stimulation, and Transcutaneous Electrical Nerve Stimulation interventions. When comparing interventions found in both studies, Aquatic Therapy, KT, Resistance Training, Tai Ji, and WBV, maintained their previous classification. Balneology and Laser Therapy were upgraded (form D to B and C, respectively). On the other hand, Acunpucture, IFC, MT, PEMF, US, and Yoga interventions were downgraded (all from B to C, except PEMF intervention which went from B to D).

Key points

- **Effective Core Interventions:** Diet Therapy, Patient Education, and Resistance Training are highly effective for KOA management.
- **Ultrasonic Therapy:** This therapy alleviates pain but lacks strong evidence compared to other treatments.
- **Moderate Support:** Aquatic Therapy, Balance Training, and Shockwave Therapy have moderate evidence for symptom improvement.
- **Variable Classifications:** Intervention effectiveness varies, with some therapies improving in classification and others, like Acupuncture, being downgraded.

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