Review Article

Understanding Knee Osteoarthritis: A Comprehensive Review

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ABSTRACT

Background: Osteoarthritis (OA) is the most prevalent type of joint disorder, with the hip, knee, and metacarpophalangeal joints, as well as the cervical and lumbar vertebrae, being particularly susceptible. Knee osteoarthritis (KOA), the most common chronic degenerative joint disease, leads to significant morbidity and disability. The increasing life expectancy and an ageing population mean that KOA not only diminishes patients' quality of life but also poses a public health challenge. Currently, there is no permanent cure for KOA. Available treatments primarily focus on alleviating symptoms and slowing disease progression. Effective management requires a strategy to address both clinical symptoms and disease progression. Initial treatment should be conservative and may include both pharmacological and non-pharmacological methods. Surgery may be considered as a last resort if conservative treatments are ineffective. This review synthesizes current knowledge on knee OA and its various treatment strategies for reducing pain and stiffness while improving patient functionality. **Objectives:** This study focuses on a comprehensive review of knee osteoarthritis and its currently available treatment modalities recommended for patients presenting with symptoms. **Methods:** A thorough literature search was carried out in search engines like PubMed and Google Scholars using following primary terms; "Osteoarthritis"; "Knee Osteoarthritis"; "Management of KOA"; "CAM therapy". Articles meeting the inclusion criteria were included in this review.

Key words: Osteoarthritis, Knee Osteoarthritis, Management of KOA, CAM therapy

Knee osteoarthritis (KOA) is a prevalent and progressive joint disease characterized by chronic pain and functional limitations. It commonly develops after the age of 40, with more prevalence in older age group. Key risk factors include advancing age, female gen- der, heavy physical activity, and prior injuries. Over recent decades, the incidence of OA in the global population of people aged above 30 years has been 14.8%, and this number is expected to continue increasing by 2050, creating a greater burden on healthcare systems worldwide [1]. OA causes significant pain and disability, which affects patients' quality of life resulting in considerable economic costs. With the ageing population and the rise of obesity, the economic impact of OA is anticipated to increase. Understanding the prevalence and risk factors of OA is vital for planning effective and cost-efficient healthcare strategies.

Further research into the disease's pathogenesis and potential therapeutic targets is essential as the new disease-modifying treatments, both conventional and complementary, could greatly benefit patients. This review aims to present current knowledge about knee OA, existing therapies that include conservative treatments (pharmacological and non-pharmacological), surgical, and complementary approaches. To compile this review, in-depth searches were conducted using well-established databases focusing on the most recent and relevant published data. The objective is to summarise current findings and provide insights into various therapeutic strategies for managing knee OA.

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KNEE OSTEOARTHRITIS

Epidemiology

Understanding the prevalence and risk factors of OA is crucial for educating the public and developing cost-effective therapies. In 2003, OA was the sixth leading cause of disability globally and was projected to become the fourth by 2020 [2]. By that year, an estimated 595 million people worldwide were affected by osteoarthritis, representing 7.6% of the global population and a 132.2% increase in cases since 1990. Projections indicate that by 2050, cases of knee OA could rise by 74.9%, hand OA by 48.6%, hip OA by 78.6%, and other forms of OA by 95.1% compared to 2020 figures [1]. In India, the situation is similar, with the number of individuals suffering from OA rising from approximately 23.46 million in 1990 to 62.35 million in 2019. Addressing risk factors such as obesity, injuries, and occupational stress is essential to mitigate the current and future impact of this condition. Epidemiological studies indicate that OA is the most common cause of pain and disability in many countries, with an overall prevalence of knee OA estimated at 28.7%, and a higher prevalence of 31.6%

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among females [3]. A cross-sectional study conducted in Kerala revealed a prevalence of 41.6% in 375 middle-aged women. Associated factors included increasing age, menopause, hysterectomy, family history of osteoarthritis, a BMI over 30, and a history of knee joint trauma [4].

Risk Factors

Risk factors for OA can be categorized into non-modifiable and modifiable types. Non-modifiable risk factors include hereditary factors, such as genetic mutations, and congenital factors, such as inherited bone shape abnormalities around the knee joint. In contrast, modifiable risk factors can be addressed through treatment. The most significant modifiable risk factor is being overweight. Excess weight places additional stress on weight-bearing joints, leading to harmful effects and promoting inflammation [5]. A review by Dong et al. identified several risk factors such as the history of knee joint trauma, overweight or obesity, female gender, and age 40 or older. Protective factors included increased physical activity and a higher level of education [6]. To alleviate the burden of knee osteoarthritis and safeguard the health of middle-aged and elderly individuals, it is essential to identify as many risk factors related to KOA as possible.

Etiology

Knee osteoarthritis is classified into primary and secondary, based on its underlying cause. Primary knee osteoarthritis occurs due to articular cartilage degeneration without a specific identifiable reason, often attributed to ageing and general wear and tear. In contrast, secondary knee osteoarthritis results from cartilage degeneration linked to a known cause. The causes of secondary knee OA can include post-traumatic factors, congenital malformations, abnormal joint positions, postoperative changes, metabolic conditions, endocrine disorders, or aseptic osteonecrosis.

Symptomatology

Key symptoms of KOA include pain, joint stiffness, decreased muscle performance, and an increased risk of disability, all of which significantly impact patients' quality of life (QoL). Compared to other chronic conditions, individuals with musculoskeletal disorders report some of the lowest health-related quality of life (HRQoL) scores, with knee OA patients showing lower scores across all HRQoL measures compared to age-matched norms [7]. Identifying therapies that enhance QoL in patients with knee OA may help alleviate the clinical, economic, and social burdens associated with this disease.

Diagnosis

The diagnosis of knee OA relies on a combination of medical history, physical examination, and radiographic imaging. Radiographs are a widely used method for assessing the severity of knee OA due to their availability and relatively low cost [9]. The severity of the disease can be classified using the Kellgren–Lawrence (KL) grading system based on radiographic findings. This classification is essential for clinical decision-making and treatment planning. The KL system was initially established using anteroposterior (AP) knee radiographs, with each radiograph graded from 0 to 4. These grades correspond to increasing severity of OA, where Grade 0 indicates no OA presence and Grade 4 indicates severe OA [10].

Table 1: Clinical Criteria for the Diagnosis of Knee Osteoarthritis [8]. ESR - Erythrocyte Sedimentation Rate; RF – Rheumatic Factor; SFOA – Synovial Fluid from Osteoarthritis

Clinical and laboratory	Clinical and radiographic	Clinical
Knee pain + at least 5 of 9:	Knee pain + at least 1 of 3:	Knee pain + at least 3 of 6:
Age > 50 years	Age > 50 years	Age > 50 years
Stiffness < 30 minutes	Stiffness < 30 minutes	Stiffness < 30 minutes
Crepitus	Crepitus	Crepitus
Bony tenderness	+	Bony tenderness
Bony enlargement	Osteophytes	Bony enlargement
No palpable warmth		No palpable warmth
ESR < 40 mm/hour		
RF < 1 : 40		
SF OA		
92% sensitive	91% sensitive	95% sensitive
75% specific	86% specific	69% specific

PATHOGENESIS

All tissues within or surrounding the joint are affected by knee osteoarthritis. The primary structures involved include articular cartilage, subchondral bone, synovium, infrapatellar fat pad, menisci, periarticular muscles and tendons. Additionally, cytokines, chemokines, microRNAs, gene expression, and other molecular factors play significant roles in the progression of the disease.

Articular Cartilage

Healthy articular cartilage maintains a balance among proteoglycans, type II collagen, water, and chondrocytes, with the latter crucial for both synthesis and repair of any cartilage damage. In OA, the upregulation of matrix metalloproteinases (MMPs), disrupts this balance, leading to a loss of proteoglycans and collagen. Initially, chondrocytes increase proteoglycan synthesis to counteract this deterioration and produce tissue inhibitors of MMPs (TIMPs). However, this compensatory response is inadequate, resulting in decreased proteoglycan levels, increased water content, disorganised collagen structure, and reduced elasticity of the articular cartilage. These changes contribute to cartilage fissures, cracking, and ultimately the abrasion of the articular surface [11].

In OA, the cartilage itself is not the sole structure affected. Cartilage lacks vasculature and innervation, which means it

does not generate pain or inflammation in the early stages of the disease. Consequently, pain typically arises from changes in the non-cartilaginous components of the joint, including ligaments, subchondral bone, joint capsule, peri-articular muscles, and synovium [12].

Synovium

The synovial membrane, along with synovial fluid, constitutes the synovium. Avascular cartilage relies on synovial fluid for nutrients and uses it as a reservoir for its degradation products [13]. In KOA, synovial fluid has been found to contain various inflammatory mediators, including plasma proteins, prostaglandins (such as PGE2), leukotrienes (like LKB4), cytokines (including TNF, IL-1β, IL-6, IL-15, IL-17, IL-18, and IL-21), growth factors (such as TGF-β, FGFs, VEGF, and NGF), nitric oxide, and additional prostaglandins [14]. These components can stimulate the production of matrix metalloproteinases and other hydrolytic enzymes, including cyclooxygenase-2 and prostaglandin E, leading to cartilage degradation through the destruction of proteoglycans and collagen [15].

Infrapatellar Fat Pad, Menisci, Periarticular Muscles, Ligaments, and Tendons

Hoffa's infrapatellar fat pad (IPFP) positioned between the synovium and the joint capsule, is situated on the anterior compartment of the knee. Its primary role is to mitigate the impact of loading forces, thereby protecting the knee from mechanical injury. The IPFP is a highly sensitive tissue composed of adipocytes, fibroblasts, leukocytes, macrophages, and various immune cells. In patients with OA, there is an increased concentration of substance P produced by innervated C fibres, which induces structural changes in the IPFP [20]. Additionally, significant levels of FGF-2, VEGF, TNF-α, and IL-6 are detected in the IPFP and synovial fluid of OA patients [21].

The loss of meniscus function contributes to OA by compromising joint stability and leading to abnormal mechanical loading [22]. When the meniscus is injured or damaged, it can result in cartilage loss, alterations in the subchondral bone, bone marrow lesions, and synovitis [23]. One of the primary functional limitations associated with knee OA is the dysfunction of the quadriceps, hamstrings, and hip muscles [24]. Increased intramuscular fat content within the quadriceps has been identified as a strong predictor of knee cartilage loss [25].

The Role of Cytokines, Chemokines, miRNA, Gene Expression, and Other Molecules

Cytokines are the primary signalling molecules involved in the immune response in OA. They are generally classified into two main subgroups based on their metabolic effects: inflammatory and anti-inflammatory. Key inflammatory cytokines include IL-1β, TNF-α, IL-6, IL-8, and IL-17, while the primary anti-inflammatory cytokines are IL-1Ra, IL-4, IL-10, and IL-13 [26]. Studies measuring IL-8 levels in synovial fluid have demonstrated a strong correlation between OA severity and MMP-13 activity; notably, a decrease in IL-8 concentration has been observed following anti-inflammatory treatment [27]. In addition to their involvement in the inflammatory response, a relationship between pain and cytokine levels has been identified, with IL-6 and IL-8 correlating with pain during movement, and TNF-α correlating with pain at rest and during movement [28].

Adipokines

Obesity is a well-established risk factor for the development of OA, with the incidence of knee OA being four times higher in obese individuals compared to those in the control group [29]. Research indicates that biomechanical and metabolic factors combined contribute to the relationship between obesity and knee OA [30].

Genetics and Epigenetics of OA

Despite the complex etiology of osteoarthritis (OA), genetic, genomic, and epigenetic studies have enhanced our understanding of the molecular processes involved. Identifying genetic risk loci associated with OA variants aids in elucidating the biological mechanisms that contribute to its development, potentially identifying targets for therapy. Among the 90 genetic loci identified in various genome-wide association studies (GWAS), 16 genes have been recognized as significant for knee OA. These include GDF5, ZNF345, SOX9/ROCR, SMG6, NF1, NFAT/WWP2, USP8, ALDH1A2, SBNO1, COL27A1, COL6A4P1, DUS4L/COG5, BTNL2, AP3B1, SDPR, and LTBP1. The predictive value of these genetic risk loci variants may serve as a useful prognostic tool for predicting the incidence and progression of OA [31].

The Role of miRNAs in Epigenetic Regulation of OA

One of the key epigenetic mechanisms involved in regulating gene expression is non-coding RNA (ncRNA) [32]. MicroRNAs (miRNAs) are a class of non-coding RNAs that bind to mRNA, thereby regulating gene expression by altering protein synthesis. This regulation occurs either through the repression of translation or by promoting mRNA degradation [33]. Research has shown that miRNAs influence several signalling pathways commonly associated with OA. Many miRNAs have been identified in tissues affected by OA, with evidence suggesting that a single gene may be regulated by multiple miRNAs [34].

Mitochondrial Genetics and Epigenetics in Osteoarthritis

Mitochondrial dysfunction has been identified in human chondrocytes affected by OA, primarily due to reduced activity of the mitochondrial electron transport chain (MRC) and altered ATP production. It is thought that mitochondrial function may be disrupted through two main mechanisms: somatic mutations in mitochondrial DNA (mtDNA) and direct effects from cytokines, prostaglandins, reactive oxygen species, and nitric

oxide. This dysfunction can lead to oxidative stress, chondrocyte apoptosis, inflammation induced by cytokines, and calcification of the cartilage matrix. These factors may serve as potential biomarkers for early detection of OA, particularly about mtDNA polymorphisms [35].

Additionally, reviews on knee OA pathogenesis indicate that the pathological changes as- sociated with the disease are not solely attributed to alterations in articular cartilage; rather, they impact nearly all tissues surrounding the joint, supporting the concept that "OA is a whole joint disease."

Management of Knee Osteoarthritis

Knee OA is among the leading global causes of disability and chronic pain. The treatment of OA requires a multidisciplinary approach, incorporating various management strategies, including patient education, self-management, non-pharmacological and pharmacological treatments, as well as surgical interventions for patients who do not respond to non-operative measures. Management options for knee OA can generally be categorized into conservative (non-operative) and surgical (operative) methods. Conservative management typically includes both pharmacological and non-pharmacological options, serving as the first line of treatment to prevent or postpone the need for surgical procedures. Additionally, complementary and alternative therapies are available for managing knee OA. The various management options are detailed in Figure 1. This review aims to provide clinicians with clear guidance and accessible resources to develop a coordinated and effective management plan that maximizes patient involvement.

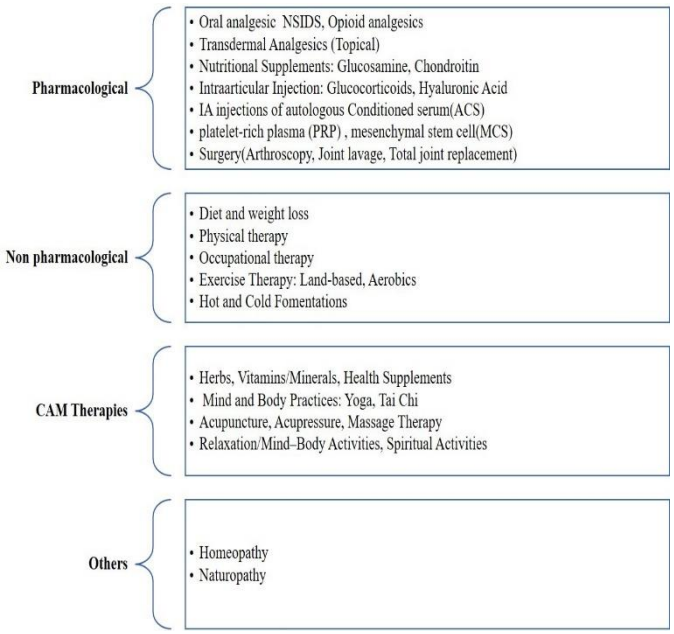

Figure 1: Various management options for Osteoarthritis

NON-PHARMACOLOGICAL OPTIONS FOR KOA

Lifestyle modification: Weight Reduction and Exercise:

Overweight and obesity are significant risk factors for knee OA [37]. Consequently, weight reduction is often one of the initial recommendations for overweight patients. According to OARSI guidelines, a moderate weight loss of 5% over a 20-week period can alleviate pain and enhance physical function [38]. Exercise is beneficial for improving knee OA symptoms; land-based exercises provide small to moderate pain relief, while water-based exercises also demonstrate beneficial effects, though quantification of these effects is lacking [39]. Systematic reviews have shown that a 10% weight loss can improve function by 28% [40].

Physical Therapy: Strength Training

Physiotherapy encompasses various physical interventions, including transcutaneous electrical nerve stimulation (TENS), low-level laser therapy (LLLT), electroacupuncture (EA), and therapeutic ultrasound (US). A systematic review and meta-analysis indicated that EA, TENS, and LLLT can reduce short-term pain (up to 4 weeks) in knee OA patients [41].

Acupuncture

The exact mechanism by which acupuncture provides pain relief in OA is not entirely clear, but it is likely associated with changes in neurotransmitters involved in pain perception. A minimum of four weeks of treatment is generally recommended, and many experts suggest more than ten sessions. Research conducted by Manyanga et al. indicated that acupuncture resulted in a significant reduction in pain and improved functional mobility, with minimal side effects reported [42].

Biomechanical Interventions: Bracing and Foot Orthoses

Non-surgical and non-drug treatments for OA that affect the medial or lateral tibiofemoral compartment can include bracing of the knee or foot. According to Raja et al.[43], knee braces and foot orthoses help reduce pain and joint stiffness. The Osteoarthritis Research Society International and the American College of Rheumatology also suggest using laterally wedged insoles for medial compartment knee OA. Knee sleeves, which provide warmth and mild compression, are beneficial in early-stage knee OA, though they do not improve joint stability. In cases of moderate to severe OA, corrective or realignment braces are more effective as they provide additional benefits by reducing compressive forces on the affected joint compartment. Bracing is generally contraindicated in cases with a flexion contracture over 10°, peripheral vascular disease, or severe contact dermatitis.

The progression of OA is often linked to biomechanical failures in the knee, such as laxity and deformities. For these patients, initial therapies for early knee OA should focus on unloading the knee joint. Minimally invasive medical devices,

including patient-specific interpositional implants and extracapsular joint unloading implants, are currently being developed to meet this clinical need [44].

Gait Retraining

Gait modification is an effective and low-cost option for OA patients, but its implementa- tion in clinical practice can be challenging. It requires a detailed assessment of pathological gait parameters due to the natural variability in gait patterns [45].

Self-Management Education Programs

Encouraging individuals to actively engage in managing their condition is a crucial aspect of care for chronic diseases. OARSI recommendations, based on meta-analyses of randomized controlled trials, suggest that self-management education (SME) programs can provide pain relief, albeit with a small effect size [46].

The pharmacological management of KOA

The pharmacological management of knee osteoarthritis primarily focuses on alleviating symptoms, which often helps maintain patient mobility. However, when symptoms become pronounced and painful, medication can be beneficial. A variety of drugs are available, particularly non-steroidal anti-inflammatory drugs (NSAIDs), often used alongside other medications, opioid analgesics, agents that promote cartilage health, and herbal products. Topical treatments are also widely favoured due to their minimal systemic side effects and high patient acceptance. Additionally, intra-articular therapies like glucocorticoids and hyaluronic acid are utilized for osteoarthritis treatment.

Analgesics

Acetaminophen is an affordable analgesic recognized as a first-line treatment for osteoarthritis (OA). It can be taken occasionally for mild pain but should not be used continuously, as it does not modify the structure of the joint. Patients are advised to limit their intake to a maximum of 4 g per day. A Cochrane meta-analysis of five randomized controlled trials (RCTs) indicated that paracetamol reduces pain by an average of four points on a 0 to 100 scale compared to placebo, with a 5% improvement from baseline [47]. However, acetaminophen did not demonstrate significant immediate effects on functional improvement, although there was a short-term enhancement of three points on a 0 to 100 scale [48].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are relatively low-cost medications that provide analgesic, anti-inflammatory, and antipyretic effects. They function by inhibiting cyclooxygenase-2 (COX-2), an enzyme involved in the synthesis of prostaglandins. There are several classes of NSAIDs available.

Acetylsalicylic acid (aspirin) belongs to the salicylate group. Ibuprofen, a derivative of propionic acid, can be administered in low doses of 400 mg three times daily or medium doses of 600 mg three times daily, with a maximum limit of 3200 mg per day. Another propionic acid derivative is naproxen, which can be given at a low dose of 250 mg three times daily or a medium dose of 500 mg twice daily, with a maximum of 1250 mg daily. Diclofenac, from the phenylacetic acid group, can be prescribed as a low dose of 50 mg twice daily or a medium dose of 75 mg twice daily, not exceeding 200 mg daily. Celecoxib is a selective COX-2 inhibitor, available in a low dose of 200 mg once daily or in medium/maximum doses of 200 mg twice daily [49].

Careful consideration should be given when prescribing NSAIDs, particularly by review- ing the patient's drug history. The concurrent use of acetylsalicylic acid and other NSAIDs increases the risk of gastrointestinal side effects, such as peptic ulcers [50]. COX-2 in- hibitors and ibuprofen are regarded as NSAIDs with the lowest incidence of peptic ulcer complications [51]. For patients with a history of high peptic ulcer bleeding, alternative therapies should be prioritized. If NSAIDs are necessary, COX-2 inhibitors can be pre- scribed alongside gastroprotective agents or a high-dose proton pump inhibitor. Addition- ally, eradicating Helicobacter pylori, which increases the risk of gastrointestinal bleeding, should be considered for patients requiring long-term NSAID treatment. In the absence of risk factors for peptic ulcer bleeding, NSAIDs can be prescribed without gastroprotective co-therapy. However, it is important to note that NSAIDs may elevate the risk of cardiovas- cular events, particularly with COX-2 inhibitors and high doses of diclofenac and ibuprofen [39]. Among NSAIDs, naproxen is associated with a lower risk of cardiovascular events [52].

Opioid Analgesics

Opioid analgesics can be administered orally, via injection, or through transdermal patches. Oral opioids are classified based on their analgesic potency. Codeine represents an oral opioid with low analgesic potency, while oxycodone and morphine have higher potencies. Transdermal opioids used for OA typically include stronger options, such as buprenorphine and fentanyl. Compared to placebo, opioid analgesics provide a notable improvement in pain, resulting in an average reduction of 0.7 cm on a 10-cm visual analogue scale. How-ever, even short-term use of opioid analgesics is linked to adverse effects [53]. The most common side effects are gastrointestinal (e.g., constipation and dry mouth) and central nervous system issues (including sleep disturbances in 25% and memory deficits in 24% [54]).

It is also important to note that opioid analgesics carry a risk of abuse, so they are generally reserved for cases where other analgesics have failed or for patients who are not candidates for surgery. Dosing for opioids in OA can be challenging; typically, patients start on low doses, which can be adjusted as needed. Tramadol is considered an atypical opioid and is associated with fewer adverse effects, such as constipation, and

has a lower potential for abuse. The recommended dosage for tramadol is 50 to 100 mg every 4 to 6 hours [55]. A randomized controlled trial (RCT) demonstrated that the transdermal fentanyl patch, which releases 25 µg/h of fentanyl, significantly reduced pain compared to placebo [56].

Topical Analgesics

Topical analgesics are effective for the localized treatment of OA when symptoms are mild. Active ingredients commonly found in topical analgesics include capsaicin and topical NSAIDs [57].

Glucosamine and Chondroitin Sulfate

A Cochrane meta-analysis indicates that glucosamine, chondroitin, and their combination result in a slight reduction in pain, averaging 0.3 to 0.5 cm on a 10-cm visual analogue scale when compared to placebo in patients with hip and knee osteoarthritis. This clinical effect is regarded as minimal [58].

Invasive Procedures Intraarticular Glucocorticoids

Glucocorticoids have demonstrated anti-inflammatory properties and can inhibit the pro- duction of collagenases, which contribute to cartilage damage in OA [59]. Intraarticular glucocorticoids are particularly beneficial for patients who do not experience improvement with non-steroidal anti-inflammatory drugs (NSAIDs). Several systematic reviews have evaluated the use of intraarticular corticosteroids in OA, yielding relatively consistent re- sults. A recent Cochrane meta-analysis encompassing 27 trials found that intraarticular corticosteroids resulted in a ten-point reduction in pain on a scale from 0 to 100 compared to placebo. This effect is primarily observed one week after injection and can last for 4 to 6 weeks. Similar improvements in function and duration of effect were noted [60].

Due to a limited number of studies, it is challenging to provide an evidence-based rec- ommendation regarding which glucocorticoid to use. The dosage varies depending on the joint being treated. For large joints such as the shoulder, knee, and ankle, methylpred- nisolone acetate or triamcinolone acetonide can be administered in doses of 20 to 40 mg (1 ml). Intraarticular glucocorticoids can be injected up to once every three months [25]. The most significant complication associated with intraarticular glucocorticoid injections is septic arthritis, although its incidence is quite low, at less than 0.08%. The most common complication is a post-injection flare, characterized by an increase in pain within 24 to 48 hours after the injection, occurring in up to 10% of patients receiving the injection [61].

Intraarticular Hyaluronic Acid

Hyaluronic acid is essential for maintaining the viscoelastic properties of synovial fluid, and its concentration is lower in OA compared to healthy joints. Supplementation with hyaluronic acid is thought to help alleviate symptoms of KOA [62]. This relatively expensive Visco supplement is available in both naturally occurring hyaluronan and synthetic forms, such as hylan GF 20. According to a Cochrane review, viscosupplements have been shown to improve pain and function by approximately 54% and 32%, respectively, in the 5- to 13-week period following injection when compared to placebo [63]. Injections of hyaluronic acid should be reserved for patients who have not responded to oral pharmaco- logic treatments and for those who are either contraindicated for or hesitant to undergo joint replacement surgery. Some authors recommend starting with glucocorticoid injections as the first-line option, and if those are ineffective, then intraarticular hyaluronic acid may be administered [64].

Mesenchymal Stem cell therapy

The goal of using stem cells is to support the knee joint cartilage's natural healing process, which can be affected by OA symptoms. The joint fluid contains mesenchymal stem cells (MSCs), which have the potential to develop into chondrocytes. In stem cell therapy, MSCs and platelet-rich plasma are collected from the patient. This process involves isolating MSCs through centrifugation and other purification steps to promote cartilage regeneration. However, there is still insufficient clinical evidence on the effectiveness of stem cell therapy compared to pharmacological treatments for OA. Some researchers have raised concerns about factors such as dosing, timing, MSC type, and methods of MSC administration in clinical studies on autologous stem cell therapy for knee OA [65].

Platelet-rich plasma

Platelet-rich plasma (PRP) is emerging as an innovative and promising approach for promoting the repair of damaged cartilage. PRP is an autologous concentration of human platelets suspended in a small amount of plasma and contains numerous growth factors that are actively released by platelets to initiate the healing of mesenchymal tissues. PRP may benefit the treatment of degenerative cartilage lesions and OA. In a randomized clinical trial, Ahmed et al. assessed the long-term impact of intra-articular (IA) injections of PRP and hyaluronic acid (HA) on clinical outcomes and quality of life for knee OA patients. At a 12-month follow-up, both groups experienced significant improvements in WOMAC pain scores and bodily pain, with the PRP group showing better results than the HA group. This study suggests that PRP is more effective in alleviating symptoms in OA patients [66].

Arthroscopy

Arthroscopic debridement is generally not recommended for the treatment of knee osteoarthritis. However, in patients with an isolated medial femoral chondral lesion, arthroscopy can offer certain benefits [67].

Joint Lavage

Joint lavage may be beneficial for osteoarthritis patients with significant synovitis, as it can help remove inflammatory

factors from the joint. However, there is a risk of serious complications, such as septic arthritis. The benefits of joint lavage in terms of pain relief are modest, showing a 0.3-cm reduction in pain and a 0.2-cm improvement in function at three months compared to the control group, as measured on a 10-cm visual analogue scale [68].

Total Joint Replacement

Total joint replacement is regarded as the definitive treatment for OA. Numerous studies have demonstrated significant improvements in pain and function following joint replacement surgery. Patients who underwent total knee replacement and subsequently participated in a 12-week non-surgical treatment program—including exercise, education, dIetary advice, use of insoles, and pain medication—experienced notable pain relief and enhanced function and quality of life after 12 months, as measured by the Knee Injury and Osteoarthritis Outcome Score, compared to those who received only the non-surgical program.

However, this surgical intervention carries the risk of serious adverse events, such as deep venous thrombosis and infection [69]. The decision to proceed with surgery should be based on the patient's clinical symptoms, preferences, and specific surgical considerations. Pain must be significant enough to cause substantial limitations in daily activities and should be unresponsive to conservative treatments like pain medications and exercise. Typically, the choice for surgery is made for patients experiencing severe pain and functional limitations, especially after reviewing joint radiographs that show severe joint space narrowing or large osteophytes.

Patients must be suitable candidates for surgery, meaning they should not have significant medical conditions that outweigh the potential benefits of joint replacement. Adequate local vascular supply and soft tissue coverage are also essential. Additionally, obesity may be a contraindication for joint replacement surgery, as it increases the risk of post-operative infections [70]. Total joint replacement is not limited to larger joints such as the knee and hip; it can also be performed on carpometacarpal and interphalangeal joints.

Recommendations from Different Societies

With the widespread availability of medical information, both patients and clinicians have access to numerous non-operative treatment options. The primary goal is to select the most relevant and suitable options based on the latest authoritative guidelines and recent high-evidence articles that have yet to be included in official recommendations. OARSI has published an evidence-based summary of recommendations that includes treatments for multijoint OA and specific options for knee OA, tailored according to the presence or absence of comorbidities.

Table 2: Societies Recommendations for Knee Osteoarthritis Management [38]; OARSI stands for Osteoarthritis Research Society International; ACR stands for American College of Rheumatology; AAOS stands for American Academy of Orthopaedic Surgeons.

Treatment	OARSI	ACR	AAOS
Exercise (land and water based)	Appropriate	Strong recommendation	Strong recommendation
Transcutaneous electrical nerve stimulation (TENS)	Uncertain	Conditional recommendation	Inconclusive
Weight control	Appropriate	Strong recommendation	Moderate recommendation
Chondroitin or Glucosamine	Not appropriate for disease modification, Uncertain	Recommended against use	Recommended against use
Acetaminophen	Without comorbidities: appropriate	Conditional recommendation	Inconclusive
Duloxetine	Appropriate	No recommendation	No recommendation
Oral NSAIDs	Without comorbidities: appropriate, With comorbidities: not appropriate	Conditional recommendation	Strong recommendation
Topical NSAIDs	Appropriate	Conditional recommendation	Strong recommendation
Opioids	Uncertain	No recommendation	Recommended only tramadol
Intra-articular corticosteroids	Appropriate	Conditional recommendation	Inconclusive
Intra-articular visco supplementation	Uncertain	No recommendation	Recommended against use

Complementary and Alternative Therapy

Complementary and alternative medicine (CAM) encompasses a diverse range of healthcare systems and practices that are intended to complement traditional Western medicine when used together, while alternative medicine is employed in place of conventional treatments. Integrative medicine combines these complementary therapies with conventional care. The

fundamental philosophy of CAM focuses on holistic care, treating the individual as a whole person. Today, CAM practices are typically categorized into five major domains: alternative medical systems, mind-body interventions, biologically-based treatments, manipulative and body-based methods, and energy therapies.

According to recent data from the National Health and Nutrition Examination Survey (NHANES), approximately 38% of adults and 12% of children have utilized CAM at some point, depending on the breadth of the definition [71]. Given that knee OA is a chronic degenerative condition characterized by pain, stiffness, and functional loss that diminishes quality of life, treatment aims to control pain and joint swelling while minimizing functional impairment. Analgesic medications are the most frequently prescribed therapies by healthcare providers and are commonly used by patients with OA. However, issues related to cost, concerns about adverse effects of analgesics, and challenges in prescribing multiple analgesics for patients with common chronic conditions present significant limitations to this treatment approach.

Traditional Chinese Medicine (TCM)

Traditional Chinese Medicine (TCM) is an ancient healthcare system that encompasses acupuncture, herbal medicine, cupping therapy, dietary therapy, and mind-body practices like Tai Chi and Qigong. It is grounded in the concept of balancing vital energy, known as ”Qi,” within the body. The mechanism behind TCM suggests that stimulating specific points on the body can modulate the flow of Qi, influencing neural pathways and neuro- transmitter release [72].

Ayurveda

Ayurveda is a holistic system of medicine originating from India, which emphasizes maintaining balance within the body through herbal remedies, dietary guidelines, yoga, and meditation. It focuses on the equilibrium of three doshas—Vata, Pitta, and Kapha—to promote health and well-being [73].

Mind-Body Practices

Mind-body practices involve techniques that enhance the connection between the mind and body to foster health and well-being. Key practices include:

1. **Meditation:** Cultivates mindfulness and relaxation.
2. **Yoga:** Integrates physical postures, breath control, and meditation, which positively influences the nervous system and enhances mind-body awareness [74].
3. **Biofeedback:** A mechanism that enables individuals to gain control over physiological functions [75].

Mindfulness practices also cultivate non-judgmental awareness, which can influence neural plasticity and support emotional regulation.

Biologically Based Therapies

Biologically based therapies utilize natural substances, such as herbs and dietary supplements, for healing. This category includes:

1. **Herbal Medicine:** Utilizes plant extracts and botanicals, with active compounds that exert pharmacological effects on biochemical pathways and physiological processes.
2. **Dietary Supplements:** Encompasses vitamins, minerals, and other nutritional products.
3. **Aromatherapy:** Employs essential oils for their therapeutic effects [76].

Manipulative and Body-Based Practices

These therapies involve the manipulation or movement of the body to address health concerns. They include:

1. **Chiropractic Care:** Focuses on the musculoskeletal system and often includes spinal adjustments.
2. **Message Therapy:** Manipulates soft tissues to promote relaxation and alleviate pain [77].

Energy Therapies

Energy therapies centre on the energy fields within and around the body to facilitate healing. Examples include:

1. **Acupuncture:** Involves the insertion of needles at specific points to balance energy flow.
2. **Reiki:** A Japanese technique that entails transferring healing energy through the hands to promote balance and well-being.
3. **Therapeutic Touch:** Involves practitioners using their hands to detect and rebalance energy fields [77].

Alternative Medical Systems

These are complete systems of theory and practice that have developed independently from conventional medicine. Examples include:

1. **Homeopathy:** Based on the principle of ”like cures like,” this system uses highly diluted substances to treat various conditions.
2. **Naturopathy:** Emphasizes the use of natural remedies, lifestyle changes, and the body’s innate self-healing abilities.

Integration of Conventional Medicine and Complementary and Alternative Medicine

The integration of complementary and alternative medicine (CAM) with conventional medicine has gained traction as both patients and healthcare providers recognize the potential benefits of a holistic approach to healthcare. This collaborative model merges evidence-based practices from both CAM and conventional medicine to improve patient outcomes.

In summary, CAM is an evolving field that encompasses a wide variety of therapeutic practices. It seeks to provide

holistic, patient-centered care by integrating traditional wisdom with scientific understanding. As the field progresses, personalized and precision approaches, along with advancements in technology, are shaping the future of CAM, contributing to a more integrated and individualized healthcare system.

CONCLUSION

Osteoarthritis is a chronic and often painful condition with no permanent cure, and it is the leading cause of mobility limitations in older adults. This review provided a comprehensive overview of knee osteoarthritis and explored various management strategies, including non-pharmacological, pharmacological, and complementary and alternative medicine (CAM) therapies. First-line treatments, such as non-pharmacological and pharmacological options, aim to delay or prevent the need for surgical intervention, which is generally reserved for patients with end-stage OA. Current literature supports a multidisciplinary, multimodal approach as the most effective strategy for managing knee OA. Various CAM therapies offer ways to relieve pain, improve functionality, and enhance the quality of life for patients, often with minimal side effects. By integrating conventional and complementary therapies, we can optimize care for knee OA patients, enhancing their quality of life and promoting whole-person health. This integrative approach not only benefits patients but also underscores the value of comprehensive care that addresses both physical and holistic well-being.

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