Review

A Narrative Review on Advances in Knee Osteoarthritis Treatment: Current Status and Emerging Trends

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Abstract

Background: The degenerative disease identified as knee osteoarthritis (KOA), otherwise known as gonarthrosis is characterized by significant clinical symptoms, which include pain, functional limitation, joint swelling, as well as a disability that lowers the quality of life. Recent years have seen an increase in the incidence of KOA, making it one of the primary reasons regarding physical disability globally. Objective: This study aims to provide a comprehensive overview of KOA from the point of view of epidemiology, risk factors, pathophysiology, diagnostic approaches, treatment options, and recent advances in the field.

Methods: A literature review was conducted systematically using databases such as Scopus, PubMed, Medline, Google Scholar and IEEE Xplore obtaining a clinical and scientific perspective on KOA. The search strategy involved using keywords such as 'osteoarthritis', knee osteoarthritis', aging', cartilage', conservative treatment', and 'intra-articular injection'. Articles were selected based on established inclusion and exclusion criteria.

Results: KOA affects quality of life with pain and limited movement that often causes depression, anxiety, and stress. KOA is prevalent in the elderly population, with risk factors such as obesity, genetics, and joint injury. The pathophysiology of KOA involves cartilage degeneration, associated synovial, and subchondral bone remodelling. Diagnostic advances through imaging and biomarkers have improved early detection. Treatments aimed at reducing pain, improving joint function, and reducing disability, include surgical, physical therapy, weight management, NSAIDs, intra-articular injections, as well as regenerative and biological therapies.

Conclusion: To improve patient outcomes, addressing the multifaceted effects of KOA is essential.

Keywords: Osteoarthritis; knee osteoarthritis; aging; cartilage; conservative treatment, intra-articular injections

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Introduction

Osteoarthritis (OA) remains the most common chronic inflammatory joint disease, which causes chronic diseases and disabilities because of pathological changes such as synovial inflammation, cartilage degradation, subchondral bone modifications, and musculoskeletal disability.[1] As per the identification of causative factors, for instance, trauma, joint surgery, malformed joints at birth, or congenital abnormalities, KOA can be classified as primary (idiopathic) or secondary. [2] Primary KOA is caused by a combination of risk factors, the most notable being increasing age and body mass index (BMI). Still, it also includes knee misalignment, heredity, greater biomechanical loading of joints, as well as low-grade systemic inflammation.

Although OA can affect numerous joints, including the hands, shoulders, elbows, knees, wrists, spine, hips, as well as ankles, among the most common and vulnerable joints is the knee. The most prevalent kind of OA, known as KOA, is very painful as well as can get swollen and stiff. Plus, it poses a serious threat to global public health. Given obesity as well as population aging, its incidence is steadily rising as life expectancy rises. According to some studies, approximately 10% of men, alongside 13% of women over the age of 60, have typical KOA. [3] In Malaysia, adults 40 years of age and older are more likely to experience KOA issues. [4]

As per Cross et al. (2014), KOA had the 38th-highest overall load as determined by years of disability-adjusted life out of 291 diseases. [5] Several studies reported that, the main effects of KOA that result in dependency and functional limitations are pain, impaired mobility, as well as physical inactivity. [6-8] Increased healthcare utilization is projected due to the heavy burden of symptoms brought on by this debilitating as well as chronic condition. Individuals with KOA may employ a variety of treatments to manage their symptoms, including medication, physiotherapy, and exercise therapy. [9] It has been shown that older individuals who have KOA utilize healthcare more frequently than people without KOA. [10]

The main KOA symptoms are pain, swelling, as well as stiffness, which makes it difficult to carry out many daily tasks like walking alongside climbing stairs. For a lot of people, it resulted in a major cause of missed work time as well as a serious disability. Pertaining to patients experiencing pain as well as impaired function, there have yet no viable pharmaceutical treatments. [11] In addition, the surgical option is costly. Despite the fact that KOA has no known cure, there are a number of treatments that may assist patients in managing their pain as well as continuing their active lives. The pathogenesis of KOA is multifactorial, with mechanical and inflammatory mechanisms being implicated. [12] It has become a major cause of pain and locomotor disability throughout the world, reducing both the quality and quantity of life. [13] KOA is thus known to cause not only physical disabilities but also mental and social dysfunction, significantly affecting the global burden of disease.

Method

A literature search for this review was conducted using several electronic databases, such as Scopus, PubMed, Medline, Google Scholar and IEEE Xplore. The search terms included keywords and phrases such as 'osteoarthritis', 'knee osteoarthritis', 'aging', 'cartilage', 'conservative treatment', 'intra-articular injections', 'regenerative medicine', and 'artificial intelligence'. The search strategy focused on identifying peer reviews articles published until 2024. Additionally, Boolean operators (AND, OR) have been used to refine the search results such as 'knee osteoarthritis' AND 'conservative treatment' OR 'non-surgical treatment'. References from selected articles were also reviewed to identify any additional relevant studies. To ensure relevance and rigor, articles in English language and studies with human subjects are included in this searching. While studies focused on other types of OA such as hip and hand, non-English articles and animals' studies are excluded.

Epidemiology

KOA mainly occurs in individuals aged ≥ 50 years. [14] It is a common chronic condition that becomes more prevalent as a result of an aging population and a rise in associated factors like obesity. There are reports that its incidence varies depending on the geographic location (10). KOA is common among the elderly in the United States, the Middle East, Europe, as well as Asia, having prevalence rates between 13% and 20%,[15] 9–17%,[16] 22% to 25%,[17] and 10% to 38% [18,19] respectively. Due to a combination of risk factors, Malaysia is also seeing an increase in the prevalence of OA. As per the Malaysian Ministry of Health, age as well as obesity are the two primary risks that raise the risk of OA, and both are rising in Malaysia. [20] Additionally, as per Department of Statistics reports from 2016 and 2019, the proportion of Malaysians aged 65 and over was estimated to be 6.7% of the country's 32.6 million inhabitants in 2019. [21] By 2040, that number is predicted to increase to 14.5%. In a cross-sectional survey from the Malaysian Elders Longitudinal Research (MELoR) research, 33.2% of

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1212 study participants reported having knee pain.[22] Malaysian National Health and Morbidity Survey 2019 found that Malaysia had a 30.4% overweight as well as 19.7% obesity prevalence. [21]

Risk factors of KOA

Understanding the risk factors for the development of KOA is important for developing prevention strategies and effectively managing the condition. The risk factors for KOA can be divided into non-modifiable and modifiable risk factors.

Non-modifiable risk factors

Age is considered the most significant risk factor for the emergence of KOA. The minimal incidence of KOA in individuals under 45 years old, estimated at less than 5%, underscores this association. The incidence of KOA exhibits a substantial increase in individuals over 65 years of age, with clinical evidence and radiological manifestations. [23]

KOA demonstrates a higher prevalence in females compared to males, particularly in those over 55 years old, with a 2:1 ratio. [24] In women, KOA is more common after menopause, suggesting a potential role of sex hormones, although no hormonal therapy administered post-menopause has been conclusively demonstrated to confer protection against OA to date. Another key study stated that the age- and sex-standardized prevalence rate of symptomatic KOA among individuals in a community health plan was 240 per 100,000 person-years, expanding significantly after age 50. [25]

Hereditary factors seem to have a role in the KOA development. Several epidemiological investigations have determined the familial component associated with OA. The genetic contribution in OA is estimated to be between 40% and 80%, with a stronger genetic contribution in the hand and hip compared to KOA. [26] Genetic investigations have revealed abnormalities.[27] There are 70 putative genes discovered in a genome-wide association study in OA, no inflammatory genes could be detected; otherwise, the growth factor cluster is strongly represented.[28] These include variants in *TGF-* β family genes, involving ligands (TGFB1, GDF5), latent binding proteins (LTBP1, LTBP3) and signaling molecules (SMAD3). The FGF family is also represented. Generally, these results underline the role of loss of reparative properties in the joint in the development of OA.[29]

Modifiable risk factors

The prevalence and incidence of KOA exhibit a close relation to body weight. While risk estimates for obesity vary, the overall evidence suggests that overweight individuals are more susceptible to developing KOA compared to non-overweight controls. Individuals who have a body mass index (BMI) higher than 30 are significantly more likely to develop KOA than people whose BMI falls between 25 and 30.[30] Another study stated that 35% increase in KOA risk with every 5-unit increase in BMI.[31]

Heavy work activity of occupation is one of the risk factors for KOA. Site-specific OA has been linked to occupations involving repetitive movement and/or heavy lifting. [32] Both men as well as women are at a higher risk of developing KOA as a result of occupational knee bending or kneeling. It has been proposed that physical activity levels could have an impact on KOA development. Long-term weight-bearing sports like weightlifting, football, tennis, as well as jogging have been linked to a higher risk of KOA. However, it remains unclear whether this association persists in the absence of sports-related injuries.[33]

Recently, notable evidence has emerged indicating mechanical pressures possess a major impact on the onset of structural damage as well as the predisposition to symptoms. The biomechanics of the knee joint can be altered by modifying intrinsic characteristics such as muscle strength and lower extremity alignment, as well as employing assistive devices.[30] Lacking vitamins D, C, as well as K are among the dietary components that have been linked to the development of KOA.[35] However, to fully comprehend the relationship between KOA and these dietary components, more investigation is required. The schematic diagram of KOA risk factors is displayed in Figure 1.

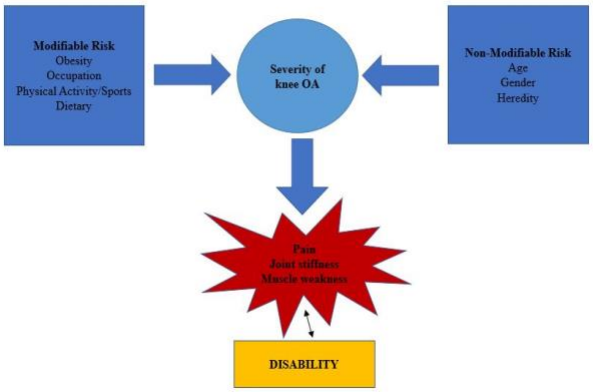

Figure 1: Schematic diagram of risk factors for KOA

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Pathophysiology

Initially, KOA was perceived as a condition solely affecting articular cartilage. However, as per current paradigms, OA is a complex disorder that affects the entire synovial joint organ. KOA is the clinical as well as pathological expression of a number of conditions that lead to both functional and structural failure of the synovial joint. These conditions include meniscal deterioration, articular cartilage erosion and degeneration, subchondral bone changes, synovial inflammation, as well as the formation of osteophytes.[36] While cartilage loss remains a characteristic feature, contemporary models underscore the involvement of the entire synovial joint complex in the pathogenesis of KOA.

Articular cartilage is hyaline cartilage, which covers the articulating surfaces of bones, is just 2–4 millimetres thick,[37] but it is vital to joint function because it allows for better joint function. It lacks lymphatics, nerves, as well as blood vessels compared to most other tissues. Water (>70%), chondrocytes, as well as organic extracellular matrix (ECM) components—primarily type II collagen, aggrecans, or other proteoglycans—makeup cartilage.[37] Its smooth, low-friction surface allows normal mobility, distributes weight uniformly, and supports joint stability.[38] However, owing to the cartilage layer's thinness, the joint's other constituents, for instance, the synovial fluid, joint capsule, synovial membrane, tendons, ligaments, as well as surrounding muscles—bear most of the loading energy.

Articular cartilage integrity is maintained by the intricate interplay of its major components: chondrocytes, aggrecan molecules, and collagens. Under normal circumstances of low-grade breakdown as well as repair, chondrocytes are known as the only cellular components of adult cartilage that control the synthesis of major ECM elements to maintain the stability of the cartilage matrix (Table 1).[37] These cells' function can be influenced by growth factors, which promote chondrocyte and proteoglycan production, and cytokines, which stimulate the production of matrix metalloproteinases (MMPs) that degrade ECM proteins.[40] Chondrocytes are the resident cell type in articular cartilage. Its derived from mesenchymal stem cells and makeup approximately 2% of the articular cartilage's overall volume.[41] The anatomical regions within the articular cartilage determine its shape, number, as well as size variations.

Aggrecan, a proteoglycan composed of a core protein as well as glycosaminoglycan side chains of chondroitin and keratin sulfate, [42,43] contributes to cartilage's compressive stiffness. These molecules form polar aggregates by binding to a single hyaluronic acid chain, retaining water. Water gets released from aggrecan molecules when pressure is introduced to the joint and is reabsorbed when the pressure is removed.

Although various collagen types are present in cartilage, type II collagen represents the most common type. [42,44] Due to their association with proteoglycans, type II collagen-containing networks in interregional regions are often resistant to degradation.[45] While collagen fibres near the basal layer anchor the cartilage and add to its tensile strength, those near the cartilage surface distribute stresses. [37,46] Additionally, collagen forms a network that entraps proteoglycans, regulating water uptake and maintaining cartilage shape.[39]

As cartilage degradation progresses, changes in the underlying subchondral bone occur. These changes include increased bone remodeling, where the subchondral bone undergoes increased remodeling, leading to the development of osteophytes (bony outgrowths) as well as subchondral bone sclerosis (increased bone density) [42] (Figure 2). Vascular invasion also occurs, where the calcified cartilage may be invaded by blood vessels from the subchondral bone, contributing to further cartilage degradation and pain. [47] Additionally, altered biomechanics take place, where variations in the subchondral bone structure can affect the joint's biomechanical characteristics, increasing the strain on the cartilage that is still present and extending the cartilage degradation cycle.[48]

In addition to the cartilage and bone changes, the synovial membrane (the tissue lining the joint capsule) becomes inflamed in KOA, a condition known as synovial inflammation. This synovial inflammation is characterized by several key features. First, there is an increased synovial fluid volume, as the synovial fluid, which normally lubricates the joint, increases in volume due to the influx of inflammatory cells and mediators.[49] Second, a condition known as synovial hyperplasia takes place in which inflammatory cells like lymphocytes and macrophages enter the synovial membrane while causing it to thicken. Third, there is a rise in the generation of pro-inflammatory cytokines as well as proteases due to the inflammatory synovial membrane, which worsens cartilage degradation alongside inflammation present in the joint.[50]

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Table 1: Histopathological changes in knee joints among the aging population and osteoarthritis (OA) patients (51).

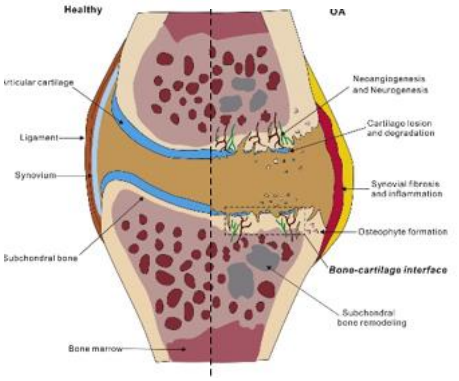
Cartilage changes	In aging population (aged 65 and above)	In OA patients
Chondrocyte size	Increased	Same
Chondrocyte count	Decreased	Same
Collagen	Same	Disorganized
Modulus of elasticity	Increased	Decreased
Proteoglycan content	Decreased	Decreased
Proteoglycan synthesis	Same	Increased
Water content	Decreased	Increased

The cumulative effects of subchondral bone changes, cartilage degradation, as well as synovial inflammation ultimately led to the clinical manifestations of KOA. These manifestations include joint pain, which arises as the cartilage wears down, exposing the subchondral bone. This exposure, along with synovial inflammation, can cause pain that is often exacerbated by weight-bearing activities and movement.[52] Additionally, joint stiffness occurs, because osteophytes and cartilage loss can restrict the range of motion as well as induce stiffness in the impacted knee joint.[53] Furthermore, KOA can lead to disability, where the pain, stiffness, and joint deformity associated with the condition can result in significant functional limitations and disability, influencing a person's capacity to carry out everyday tasks.[54] This table 2 summarizes the main changes that occur in the pathophysiology of osteoarthritis of the knee compared to the healthy knee joint, highlighting differences in structure and function that contribute to the development of the disease.

Current research has emphasized the critical role of low-grade chronic inflammation in KOA, comprising pro-inflammatory cytokines for instance IL-1β, TNF-α, and IL-6, which stimulate the production of MMPs and aggrecanases, promoting cartilage degradation.[40] In addition, advanced imaging and molecular studies have revealed that early subchondral bone remodeling, synovial angiogenesis, and nerve sensitization are central contributors to both joint damage and pain perception in KOA.[47] As such, targeting inflammatory pathways and nerve growth factors (e.g., NGF inhibitors) have emerged as therapeutic strategies aimed at altering disease progression and pain in KOA.[36,55]

Furthermore, regenerative medicine approaches, including stem cell therapies and the use of growth factors like platelet-rich plasma (PRP) and bone marrow-derived mesenchymal stem cells (BM-MSCs), have shown promise in modulating the joint environment. These treatments aim to enhance cartilage repair, reduce inflammation, and restore joint function by promoting anabolic processes within the cartilage and the synovial membrane.[56,57] Ongoing efforts to incorporate biologics and gene therapies to modulate chondrocyte function and ECM synthesis represent potential future directions in improving KOA management.[34,39] Therefore, understanding the pathophysiology of osteoarthritis is important for personalized prevention and treatment strategies, with lifestyle modifications and physical activity potentially reducing the need for surgical intervention.

Table 2: Changes in Pathophysiology of KOA Compared to Healthy Knee

	Healthy knee	KOA
Figure (adapted from Yuan et al, 2014)		
Articular Cartilage	Maintains integrity with a smooth, low-friction surface; primarily composed of chondrocytes, aggrecan, and type II collagen.	Shows erosion and degeneration; cartilage becomes thinner, leading to increased friction and impaired joint function.
Chondrocyte	Chondrocytes regulate ECM synthesis, maintaining cartilage stability through a balance of synthesis and degradation.	Chondrocytes become dysfunctional, leading to increased production of matrix metalloproteinases (MMPs) and aggrecanases, promoting degradation.

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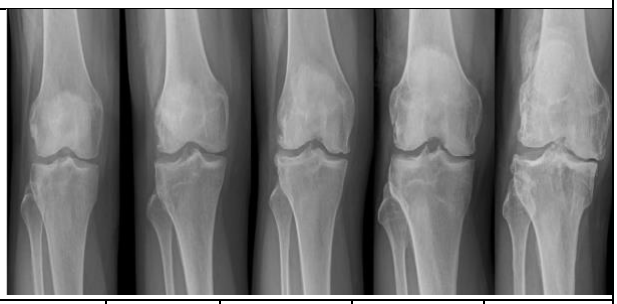
	Healthy knee	KOA
Aggrecan and Water Content	Aggrecan retains water effectively, providing compressive stiffness and shock absorption during joint loading.	Decreased aggrecan content and water retention lead to reduced compressive properties and increased stiffness.
Subchondral Bone	Remains stable with normal remodeling processes; supports cartilage without significant changes.	Increased remodeling leads to osteophyte formation, sclerosis, and vascular invasion, contributing to further cartilage degradation.
Synovial Membrane	Healthy synovial membrane maintains normal fluid volume and lubrication without inflammation.	Synovial inflammation occurs, characterized by increased fluid volume, hyperplasia, and elevated pro-inflammatory cytokines.
Joint Mobility	Full range of motion with no restrictions; joint stability is maintained.	Limited range of motion due to osteophytes, cartilage loss, and joint stiffness; functional limitations are common.

Clinical diagnosis and classification systems

KOA can be diagnosed clinically and radiologically. It is a clinical condition characterized by objective physical examination findings of knee stiffness, deformity, stiffness, subjective feeling of joint discomfort on load and bone enlargement, and additional radiological findings.[58] Radiographic indicators for major KOA include subchondral sclerosis, osteophyte formation, cyst formation, as well as nonuniform joint space loss. It is possible that the initial radiographs do not reveal all the abnormalities. Plain film radiographs are typically adequate for the initial radiographic evaluation required to validate the diagnosis or assess the severity of the disease. The benefits of radiography are clear: they are very accessible, reasonably safe, as well as cost-effective. Nevertheless, there may not always be a correlation between subjective pain and radiographic changes.[59]

Pertaining to KOA diagnosis, plain radiography remains the gold standard and an acceptable quantification tool to assess KOA severity. The earliest official attempts to create a radiographic classification scheme for OA were reported by Kellgren and Lawrence (KL) in 1957.[60] Anterior-posterior (AP) knee radiographs were initially used to define the KL classification, and each radiograph was given a grade between 0 and 4 (Table 3). In the early stages of KOA, subtle changes may occur that lead to findings that may overlap with other knee pathologies.[61] With reference to the scale of KL, traditional methods struggle to identify early stages of KOA where changes may be subtle causing potential delays in diagnosis and treatment.

Table 3: Multiple kinds of Kellgren and Lawrence classification system variants. [60,62]

Kellgren-Lawrence Grading Scale					
Radiological image					
Classification	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	None	Doubtful	Minimal	Moderate	Severe
Description	Definite absence of x-ray changes of osteoarthritis	Doubtful joint space narrowing and possible osteophytic lipping	Definite osteophytes and possible joint space narrowing	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis, and possible deformity of bone ends	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

The use of artificial intelligence (AI) in KOA has increased significantly in the last decade. [63-67] AI and machine learning (ML) modeling is a new decision-making tool in KOA diagnosis, preprocedure planning for total knee arthroplasty (TKA), disease progression and treatment outcome estimation greater with technological advances making these tools better, but thorough validation is still needed. Recent studies have

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proven that AI models can achieve high accuracy in diagnosing KOA from radiographic images. For example, Convolutional Neural Networks (CNNs) has been used to assess the KL grade of KOA with comparable performance to radiologists.

A study by Tiulpin et al. demonstrated that the deep learning (DL) model could automatically grade knee radiographs with high accuracy, suggesting potential for clinical use.[68] AI models have also been developed to predict the progression of KOA, helping doctors identify patients at high risk for rapid disease progression. In this case, the model developed by Li et al. used clinical and imaging data to predict the risk of KOA progression over several years, offering tools for personalized treatment planning.[69] AI is also used to tailor treatment plans based on individual patient data, including genetic, clinical and imaging information. This approach aims to improve outcomes by providing personalized therapeutic strategies. Research conducted by Guan et al. focused on the integration of multimodal data to develop personalized treatment plans, showing promise in improving patient-specific outcomes in the management of KOA.[70] Furthermore, interpretability and transparency of AI algorithms are essential to gain trust from doctors and patients.

Treatment

Both non-surgical and surgical treatment options are available for KOA (Figure 2). The choice of treatment depends on patient-specific factors such as the duration of the disease, the intensity of the pain, and the presence of comorbid conditions.[71] The first-line treatment for KOA does not involve surgical intervention, and management may be multimodal. However, if these therapies are ineffective, one must consider surgical treatment. Although KOA has no cure, there are several surgical and non-surgical treatment options available to assist in reducing pain, maintaining the health of affected patients and significant deterioration.[73] This has created a challenge for health care professionals to find the best treatment.

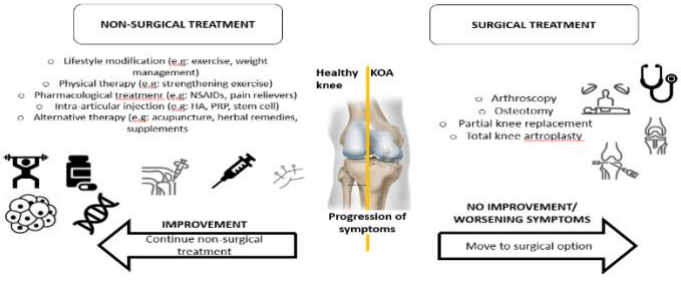

Figure 2: Non- surgical and surgical treatment for KOA

Non-surgical

Non-surgical treatment aims to educate patients, reduce pain, slow disease progression, and enhance functional capacity. Patients are encouraged to change their lifestyle, including engaging in appropriate exercise and controlling their dietary intake. Low-impact sports consisting of swimming and cycling are advised, but high-impact ones like jumping and running on hard surfaces should be avoided. For those who have patellofemoral OA, squatting and stair climbing should be avoided. Patients who are obese should be advised as well as given encouragement to lose weight. Weight management plays an important role in symptom management, and it has been observed that the benefits of exercise are amplified by weight reduction.[70] Obesity can predispose patients to suffer from KOA, it has deleterious molecular and mechanical effects. Adipose tissue itself is a source of inflammatory factors. Cytokines adipokine, IL6, TNF alpha and C-reactive protein are elevated in the plasma of obese patients and have been associated with changes in cartilage homeostasis and degeneration.[75]

The clinical application of physiotherapy enhances blood circulation, provides anti-inflammatory and analgesic effects, and helps to reduce symptoms.[76] Physiotherapy techniques used in the treatment of KOA include hot compresses, aquatic therapy, acupuncture and electromagnetic and ultra-short-wave therapy.[77] Physiotherapy incorporating muscle strengthening and an aerobic exercise regimen is effective in the therapy of KOA.[78] Range-of-motion exercises can assist in preventing the formation of contractures. Exercises that strengthen the periarticular muscles contribute to stabilizing the knee and alleviating pain.

Current pharmacological therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs) are palliative because their main purpose is to relieve the symptoms of inflammation and pain which will slow the progression of the disease.[79] In cases of pain exacerbation and knee swelling, NSAIDs are recommended.[80] These medications inhibit pro-inflammatory mediators, for instance, prostaglandins as well as leukotrienes by reversibly blocking the cyclooxygenase and lipoxygenase pathways. There is a wide range of NSAIDs available; the choice should be made with cost-effectiveness, patient acceptability, as well as medical considerations in mind.

Tenoxicam is an effective analgesic and anti-inflammatory drugs for the symptomatic treatment of KOA that give chondroprotective effect. Apart from

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oral use, tenoxicam is also used as an intra-articular treatment because it is water soluble and not requires a solubilizing agent unlike most injectable NSAIDs preparation option which can minimize the gastrointestinal side effects of NSAIDs.[81] In addition, there are previous studies that compare the effectiveness of oral and intra-articular tenoxicam in the treatment of KOA. They suggest intra-articular tenoxicam is as effective as oral tenoxicam and can be considered as an alternative treatment in KOA.[82] An experimental study producing OA in rats by transection of the anterior cruciate ligament and medial meniscectomy; Ozkan et al. states that the effect of tenoxicam is similar to hyaluronic acid (HA) to protect cartilage structure and also proteoglycan content.[83]

Intra-articular corticosteroid injections can provide symptomatic relief for KOA, especially if there is a lot of inflammation and the most common conservative approach in treatment of KOA. Direct corticosteroid administration into the knee may lessen OA-related local inflammation while minimizing systemic steroid effects. Its as an adjunctive treatment for moderate -to-severe KOA. HA injections into the joints are another injectable treatment option for KOA. The human body contains HA, a glycosaminoglycan, in both articular cartilage and synovial fluid. Over the past three decades, these injections have been widely used for pain relief in KOA patients. As OA worsens, HA deteriorates in addition to causing articular cartilage degradation, stiffness, as well as pain. [84] The purpose of HA injection is to increase the amount of intra-articular volume in the synovial joint which can reduce the intensity of friction between the articular surfaces. It functions as a lubricant that will increase the viscosity and elasticity of the synovial fluid; thus, this will reduce pain and further cartilage damage caused by KOA.[85] The latest HA formulation with added higher molecular weight aims to improve joint lubrication and reduce inflammation more effectively. A major concern of HA treatment is the wear-and-tear effect over time, which requires frequent administration for temporary pain relief.[86] Therefore, the search for regenerative medicine is the main stream of alternative treatment for KOA patients.

Platelet-rich plasma (PRP), also known as autologous conditioned plasma (ACP), as the name suggests, is obtained from oneself and provided for therapeutic purpose. Its effectiveness has been studied for the past two decades.[87,88] With the anti-inflammatory properties found in PRP this can reduce the level of systemic inflammation in KOA by inhibiting the release of matrix metalloproteinase (MMP-9) and cytokines such as tumour necrosis factor (TNF-α) and interleukin (IL-1β). [89] PRP was administrated through intra-articular injections.

Over the past decade, various trials have been studied to find out the feasibility of using Mesenchymal stem cells (MSCs) as an advanced treatment option for regenerative medicine in treating KOA and other structural damage.[90] Often, adipose tissue is used as a source of MSC because of its abundance and accessibility in the human body. In other studies, bone marrow and umbilical cord were used to exploring and comparing the effectiveness of stem cells from different origins.[91] Both intra-articular PRP and MSC injections are effective in patients with mild to moderate KOA. It provides symptom relief, restores physical function and increases tissue repair potential in affected joints. PRP treatment worked best among patients with KOA KL grade I-II, while MSC treatment worked best among the group of KOA KL grade II-III. Both treatments showed minimal effects in patients with severe KOA KL grade IV. Regenerative medicine has shown promising results in both therapeutic efficacy and safety when compared to traditional conservative treatments such as HA injections. However, the mechanism of action of PRP and MSC is still unclear and requires further research to establish a standardized preparation method, optimal dose determination and frequency of use.[91]

The approach in stem cell therapy for cartilage replacement involves multiple steps that is currently already at the scaffold optimization prior to massive clinical trials in the future. The procedures initially require the harvest of stem cells from multiple joint sites from symptomatic OA which then will be engineered to a suitable scaffold. Subsequently, the scaffolded cells will then be transferred for an ex vivo cartilage formation before implantation or replacement of the damaged cartilage can be done (Figure 3).[92] Recent advancements show that the chondrocytes are possibly able to be reproduced in vitro – the lab produced scaffold is called as micro-cartilage model chondrogenic spheroids. Ideally, the current scaffold technologies have evolved to a stimuli-responsive smart scaffold, 3D-printed scaffolds and cartilage bionic scaffolds.[93] A recent study by a Japanese group on engraftment of allogenic iPSCs derived cartilage organoid in a primate model showed a highly promising data with production of hyaline cartilage-rich tissue in the chondral defects within 4 to 17 weeks post-surgery, however the exposure to abundant blood flow may cause trigger to the immune system thus further studies are warranted. Despite that the study further shows definitively that chondral

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defects can be treated by allogenic cartilage transplantation.[94]

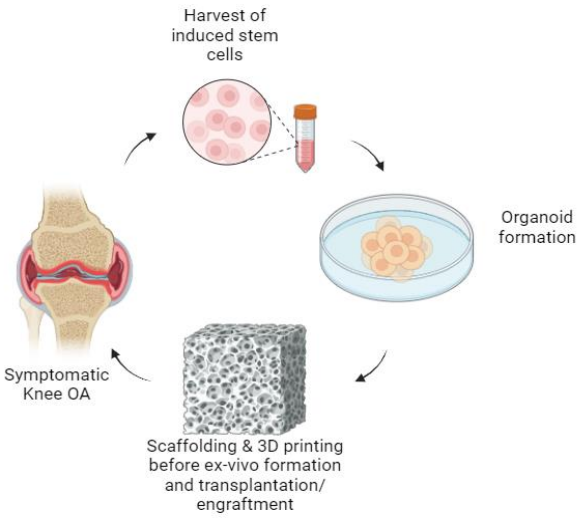

Figure 3: A simplified summary of procedures necessary in development of iPSC transplantation in knee OA

Next, complementary and alternative medicine (CAM) which refers to techniques that are integrated with or replaced by traditional western medical practices. In recent times, with the continuous development of CAM research, it has achieved significant results in the treatment of KOA. A growing number of researchers are studying the use of CAM approaches to treat KOA, including acupuncture, moxibustion, Tuina, Chinese herbal medicine, yoga, Baduanjin and Tai Chi.[95,96] Evidence from clinical trials shows that acupuncture and Tai Chi mind-body therapy are safe and effective treatments for KOA. An integrative approach combines the best of conventional medicine and CAM therapies to ultimately improve patient care. These modalities may lead to the development of better disease-modifying strategies that may improve symptoms and reduce the progression of KOA. Currently there is no drugs that halt the progression of the disease or reverse the pathological changes in the entire joint and most patients with late-stage KOA require surgical treatment.[97]

Surgical

Surgical treatment is recommended for patients with advanced KOA who have a poor response after 6 months of receiving conservative treatment, and whose condition severely affects daily life. [98] Surgical treatment options for KOA consist of cartilage repair, arthroscopy, osteotomy, as well as knee arthroplasty. [99] The selection of the most appropriate surgical intervention is influenced by factors such as the location and stage of KOA, the presence of comorbidities, and the degree of patient impairment. The primary objectives of surgical treatment for KOA patients aim to lessen or eliminate pain, lessen disability, as well as boost the quality of life.

In theory, arthroscopy for KOA aims to improve symptoms by removing debris and inflammatory cytokines that lead to synovitis.[100,101] Torn meniscal fragments, as well as loose flaps of cartilage, can be removed with debridement (removal of frayed cartilage or partial meniscectomies). However, evidence suggests that arthroscopic lavage (joint irrigation) provides only short-term benefits for a limited subset of individuals with mild radiographic OA as well as effusion. Damaged articular cartilage has little to no capacity to regenerate. Procedures for cartilage repair are only recommended for focal cartilage defects, which may represent a precursor of KOA. Once the defect extends beyond the cartilage, it is no longer recommended to repair.

For unicompartmental OA of the knee, osteotomy has become the usual course of treatment. It is a procedure that involves breaking and then realigning bone. This was the method that was most commonly used for a long time. The popularity of osteotomy around the knee decreased in the 1980s and 1990s due to knee arthroplasty's favorable outcomes. Osteotomy was seen as a more difficult procedure with a higher chance of complications and unknown results than arthroplasty.[102]

Nowadays, the current treatment by combining osteotomy with biological agents like PRP or stem cells is a novel approach to delaying the need for joint replacement in younger patients. Typically for late-stage KOA, total or partial knee replacement remains the solution to provide long-lasting pain relief and functional improvement. The choice for partial and total knee replacement depends on the degree of joint involvement, with unicompartmental knee arthroplasty being the option for more localized damage.[103]

Research is underway into gene therapy targeting specific genes responsible for cartilage degeneration, and tissue engineering approaches aimed at growing new cartilage in the laboratory for transplant purposes. These treatments show promise, although some are still in the experimental or early clinical stages. Depending on the severity or KL grade of KOA and the patient's overall health, a combination of therapies is often recommended to obtain optimal results.

Implications of the findings from this review

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Findings from this review highlight important implications for policy, clinical practice, and research in knee osteoarthritis (KOA). Policy makers are advised to prioritize funding and develop clear regulatory guidelines to support and implement the ethics of new therapies such as regenerative medicine, biologics, and gene therapy. Public health initiatives that focus on modifiable risk factors such as obesity as well as promoting early detection through awareness campaigns are important in reducing the burden of KOA. In clinical practice, the integration of conservative management and advanced therapy through a multidisciplinary care model has the potential to improve patient outcomes, while technologies such as AI-based diagnostics and wearable devices can monitor disease and personalize treatment. Future research should pay attention to the long-term efficacy, safety, and effectiveness of new therapies, while improving the understanding of the pathophysiology of KOA to identify new therapeutic targets. Standardization of biomarkers and diagnostic tools should also be strengthened to support early detection and disease monitoring. Additionally, addressing gaps in access to advanced treatment and ensuring healthy healthcare delivery is critical to improving global outcomes in the management of KOA.

Strengths and limitations of this review

This review provides a comprehensive overview of KOA by synthesizing evidence including epidemiology, risk factors, pathophysiology, diagnostic approaches, treatment options, and recent advances. The main strength of this study is the focus on new trends such as regenerative medicine and AI applications, which offer future insights for doctors and researchers. The integration of traditional and modern approaches also increases the practical relevance of this study. However, the narrative nature of this review limits the quantitative analysis and may introduce selection bias due to being based on specific databases and English-language studies. Moreover, discussions about innovative treatments still lack emphasis on cost-effectiveness and scalability. Finally, rapid development in this field may affect the durability of some conditions. Despite these limitations, this study remains an important reference source for understanding KOA and guiding future research and clinical practice.

Conclusion

Despite being one of the most prevalent and extensively researched knee disorders, OA lacks a well-defined pathophysiological mechanism and a universally effective treatment approach for alleviating symptoms and mitigating associated joint damage. In the early stages of KOA, exercise therapy has been established as an effective conservative management strategy. A range of non-surgical interventions, such as intra-articular injections, bracing, and physical therapy, demonstrate variable efficacy, with outcomes influenced by numerous factors, including equipment quality, provider expertise, and patient characteristics. Consequently, the judicious selection and implementation of these modalities necessitate careful consideration of the individual clinical scenario. In cases of advanced KOA requiring surgical intervention, biological fixation techniques have become a viable method to increase durability with regard to total knee arthroplasty, particularly in younger patients. This development is driven by advancements in biotechnology and the availability of biomaterials with improved osteoconductive properties, fostering better osseointegration and implant longevity.

Declarations

Authors' contributions: MMG and MRAMZ made substantial contributions to the conception and design of the study and acquisition of data. SI, MMG, ZMMZ and MRAMZ contributed substantially to data analysis. MMG drafted the manuscript, and SI,ZMMZ and MRAMZ revised it critically for important intel lectual content. All authors approve the final version submit ted for publication and agree to be accountable for all aspects of the work and take responsibility for statements made in the published article.

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