

Review Article

New Horizons in Treatment of Knee Osteoarthritis: A Brief Look-up at Emerging Approaches

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Abstract

Knee osteoarthritis (OA) is a chronic and prevalent musculoskeletal condition that is the underlying cause of disability in most patients worldwide. Even though the pathophysiology of KOA has not yet been fully understood and includes a wide range of risk factors, current therapeutic options are temporarily palliative rather than curative. In recent years, new strategies have focused on the curative agents. As part of this review, we highlight the latest treatment approaches for KOA.

Keywords: osteoarthritis, mesenchymal stem cell, exosome, regeneration medicine, scaffold, immunotherapy, machine learning

1. Introduction

Osteoarthritis (OA), which was previously known as wear and tear, is a degenerative disease involving the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane, and periarticular muscles [1, 2]. The term OA is derived from the Greek words osteo (bone), arthro (joint), and itis (inflammation) [3]. OA could affect any synovial joint; however, it typically occurs in the knee, hip, hand, ankle, foot, and spine. The knee is the most common joint affected by OA [4]. According to statistics, approximately 50% of the world population over 65 years is affected by OA [2]. During the

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development of knee OA (KOA), articular cartilage and its surrounding tissues are locally damaged. In the etiology of this condition, genetics, environment, and epigenetics play a critical role, and their interaction results in a complex pathology [5, 6]. The methods for diagnosing a disease vary at each stage of the illness. Advanced machine learning and deep-learning techniques offer reliable means for early diagnosis and prognosis of OA [7]. Unfortunately, the current therapy choices for OA patients are temporarily palliative rather than curative. However, the pain and physical limitations associated with OA often cause disabilities. The administration of the drugs in combination with a non-pharmacological regimen is the most effective for OA pain management. Nonetheless, there are concerns about the adverse effects of these drugs on the human body, including liver and renal toxicity, and cardiovascular and gastrointestinal disorders [8, 9]. Surgery could be the last option when the pharmaceutical and non-pharmacological regimens fail to treat symptoms in individuals with severe OA [10, 11]. In order to combat the progress of OA at an early stage or trigger the regeneration of articular tissues, new therapies are needed greatly [2]. Recently, special consideration has been paid to the role of the immune system, metabolic pathways, and regenerative medicine in new treatment strategy. This review discusses about new therapeutic horizons.

2. Epidemiology of OA

OA was the 11th most significant worldwide disability, contributing to 291 health problems examined in the Global Burden of Disease (GBD) 2010 study, impacting physical and mental health and resulting in notable healthcare costs [12]. KOA affects approximately 7% of the global population, more than 500 million people worldwide [13, 14](11). According to the Global Burden of Diseases study, the incidence of OA rose by 8.2% between 1990 and 2017, with 303.1 million prevalent cases [15, 16, 17]. Indeed, the prevalence of OA in Europe is estimated to be 10–17%, 12–21% in North America, 2–4% in South America, and 16–29% in Asia, Africa, and Middle Eastern countries [18]. In Asia, about one million people have been affected with OA in Yemen, Iraq, Syria, and Saudi Arabia [19]. According to some reports, the global prevalence of KOA was 160% in people aged 15 and older; moreover, in those over the age of 40, it was 229% [20]. Furthermore, the global prevalence of symptomatic OA is estimated to be 9.6 and 18% in men and women, respectively [21]. In central Asia, Kazakh Females have been reported to show a lower incidence of KOA than males until the age of 45. According to Kazakhstan's job and labor data, most males worked in agriculture, forestry, industry, and construction have a higher risk of OA due to intensive labor and continuous stress on certain joints [22, 23].

3. Symptoms of KOA

KOA is a prevalent condition that causes pain around the knee joint that can range from minor to severe. This painful condition might appear gradually or unexpectedly, which worsens with use and gets better with rest. With heavy exercise, joint discomfort and stiffness usually subside within 30 minutes, a process known as gelling [6, 24]. Patients in advanced stages may exhibit symptoms of instability, with varus deformity being the most frequent [25].

4. Etiology of KOA

KOA is categorized as either primary (early-onset, idiopathic) or secondary (late-onset), depending on its underlying cause [2]. The hyaline joint cartilage, a major component of the knee joint, is the primary site of the deteriorating factors that lead to OA and the structure where the illness first manifests [26]. Primary KOA is the result of articular cartilage degeneration, but the reason is unknown. Posttraumatic, postsurgical, malposition (varus/valgus) [27], scoliosis [28], rickets [29, 30], hemochromatosis [31], chondrocalcinosis [32], ochronosis [33], Wilson disease [34, 35], gout [36], pseudo gout [37], acromegaly [38], rheumatoid arthritis [39], hemophilia [40], paget disease [41, 42], and sickle cell disease [43] are among the common underlying reasons for secondary KOA [44, 45].

5. Risk Factors

The prevalence of KOA has differed among reports depending on age, gender, region, body mass index (BMI), and other potential etiologies of KOA [20, 46]. Unmodifiable risk factors for KOA include age, gender, and genetics. Changes in the cartilage matrix with age and chondrocyte senescence contribute to age-related OA. Because aging is a systemic process, identifying common processes will lead to novel approaches that decrease the aging process and slow the progression of OA [47, 48]. Among different age groups, most adults who are 65 and above are at a higher risk of developing this disease [6]. The incidence of KOA is higher in females than males [46]. Women are more severely prone to KOA because of variations in anatomy, kinematics, and hormonal factors [49]. Early-onset OA is strongly influenced by genetic factors as far as the research demonstrates a 39–65% effectiveness of genetics on radiographs of OA in the hands and knees, regardless of environmental and demographic factors [50]. Studies on candidate genes focused on chondrocyte cell signal transduction,

bone mineral density (BMD), and genes involved in cartilage structure [51]. Women prone to KOA and ESR1 gene (estrogen receptor 1) variants [Pvull (rs2234693) and Btgl (rs2228480)] have been identified as critical risk factors [52]. Generic loci and variations have been evaluated by genome-wide association studies (GWAS), which aid with early diagnosis and medical care [53, 54]. DNA methylation, expression of non-coding RNAs (ncRNAs), long non-coding RNAs (lncRNAs), and short nucleolar RNAs (shnRNAs) are the three processes through which epigenetics regulates gene expression and the pathogenesis of OA [55, 56, 57].

Modifiable risk factors of KOA include pathophysiological factors (hypertension) [58], type 2 diabetes [59], higher bone mineral density (BMD) [60], lifestyle factors (obesity) [61], smoking [62], loading joints [63], environmental factors (poor home ventilation and heating) [64], and socioeconomic factors (lower education, separation, divorce, or death) [65].

6. Diagnosis

KOA is a common condition that can be diagnosed using clinical findings or a combination of clinical and radiographic findings. It is important to consider the underlying disorders like trauma, congenital or developmental disorders, calcium pyrophosphate dihydrate deposition disease, and other bone and joint disorders. Posttraumatic OA, caused by previous fractures, accounts for only 12% of the symptomatic OA [66, 67]. A clinical diagnosis is supported by typical symptoms, physical examination findings, laboratory results, and imaging features. A focused physical examination should be conducted to assess tenderness, pain, ambulation, and injury to surrounding muscles, tendons, and ligaments [6, 68, 69]. KOA usually causes pain in one or both knees, and it most commonly affects males in their 40s or older, as well as women in perimenopause or older. Symptoms emerge gradually. The pain is frequently boring involving the entire knee or a smaller area, and can occur when at rest or at night, interfering with sleep. Crepitus, bone enlargement, decreased knee flexion, flexion contracture, soreness, erythema, warmth, and swelling are some of the symptoms reported in the clinical history. Other joints should be checked to rule out OA [70]. Radiologic evaluation may be used, but the American College of Rheumatology suggests a secure diagnosis without radiologic evidence. There are no blood or urine tests available to diagnose OA, and joint aspiration is not usually recommended [69, 70]. To evaluate articular tissue, many image modalities such as ultrasound, radiography, and magnetic resonance imaging (MRI) and Computed tomography (CT) are employed. Ultrasound may visualize superficial soft tissue structures but causes cartilage damage and bias. The

gold standard for disease-modifying OA medication studies is radiography, however, it has limitations. MRI is non-invasive, objective, reproducible, change sensitive, and can detect changes in knee tissue before radiography evidence. MRI technology generates high-resolution pictures that detect soft tissues and bones and allow them to be visualized. Scoring and manual, semi-automatic, and fully automated quantitative systems are among the MRI knee tissue evaluation methods. Despite low tissue contrast and radiation exposure, CT is a reliable bone assessment technology with quick scanning time and good spatial resolution [71, 72]. New studies have shown that machine learning has the ability to automate the diagnosis and prognosis of KOA, leading to increased accuracy, efficiency, and repeatability. Through the use of AI-assisted models, we can now predict the onset and progression of OA, as well as changes in pain levels and physical structure. Despite some limitations in research, machine learning holds great potential for early detection, future prediction of the disease, and identification of new imaging characteristics and markers for its status. With ongoing advancements in model development, this technology could lead to novel therapeutic options. [71, 73, 74].

7. Pathogenesis of KOA

KOA is a complicated process including inflammatory and disordered metabolic components. The pathophysiology of OA is strongly influenced by inflammation, including systemic inflammation and active synovitis [75]. Low-grade, chronic inflammation of the synovial lining is a key factor in defining OA pathophysiology, a common symptom in OA patients [18, 76]. Pro-inflammatory mediators like cytokines, lipid mediators, and reactive oxygen species (ROS) impact the extracellular matrix, leading to cartilage degradation [77]. OA tissues showed increased levels of pro-inflammatory cytokines like IL-1, IL-6, IL-15, IL-17, IL-18, TNF-, and LIF, while antioxidant enzymes decreased in OA patients [78]. Damage to cellular and cartilage ECM may trigger molecular patterns that interact with TLRs, triggering the innate immune system and causing a sterile inflammatory response [79]. Increased TLR-2 and TLR-4 levels in synovial tissue, articular cartilage lesions, and synovial membranes of OA patients lead to overexpression of matrix metalloproteases, nitric oxide, and prostaglandin E2. All of these gradually aggravate the inflammation and accelerate the destruction of the cartilage tissue (Figure 1) [18].

7.1. The role of the immune system in the pathogenesis of KOA

OA is a degenerative disease that can be caused by genetic, metabolic, or mechanical reasons. The first damage results in cartilage-specific auto-antigens, which activate

the immune response. This results in the production of cytokines and chemokines, activation of the complement system, and the release of cartilage-degrading proteins, which continue to damage the articular cartilage [80].

7.1.1. Innate immunity

Macrophages, which are present in inflamed synovium, play a key role in OA by producing cytokines such as IL-1 and TNF- α , contributing to cartilage destruction [81, 82]. Synovial macrophage depletion can reduce TGF-induced osteophyte development, although macrophage activation is required for MMP synthesis and cartilage degradation [82, 83, 84]. The complement system, a critical effector of the immune system, is implicated in the activation of complement factors in OA cartilage. During OA, chondrocytes overexpress the C5a receptor [85, 86]. Cytokines including IL-1, IL-6, and TNF- alter the anabolic and catabolic processes, resulting in cartilage deterioration [87, 88, 89]. Chemokines, which are small secretory molecules that regulate immune cell chemotaxis, are also highlighted in OA, with some being overexpressed in human chondrocytes and causing cartilage destruction. During arthritis, the presence of chemokines in diseased synovial fluid may stimulate mesenchymal progenitor cell migration [80, 90].

7.1.2. Adaptive immunity

Synovial tissues from OA patients include CD3⁺ T cells, with Th1 subsets being five times more prevalent than Th2 cells [91]. T-cells in the OA synovium exhibit indicators of early, moderate, and late activation, indicating an active immunological response. MIP-1 synthesis, macrophage infiltration, and MMP-9 expression are all increased by CD4⁺ T cells [92]. Activated B lymphocytes are seen in inflamed OA synovium, indicating antigen-driven activation. Autoantibodies to cartilage-derived proteins such as osteopontin and collagen have been linked to cartilage degradation [93, 94].

7.1.3. TLRs signaling pathways

TLRs, motif recognition receptors, initiate an innate response against pathogens. They are expressed on immune cells and activated upon tissue injury [95]. Joint damage in OA releases DAMPs, activating TLRs. TLR activation leads to catabolic pathways in chondrocytes, triggering pro-inflammatory cytokine production from macrophages [95, 96].

7.1.4. NF- κ B signaling pathways

The transcription factor NF- κ B modulates inflammation, immunological response, and apoptosis. It is essential for cartilage metabolism and the development of OA [97]. NF- κ B overexpression suppresses inflammatory responses. In OA drug development, small molecules or siRNA are commonly used to inhibit NF- κ B activation [98, 99].

7.1.5. Metabolism pathways

Because of the hypoxic environment in which they live, chondrocytes are extremely dependent on glycolysis as their main energy source, demonstrating a close association between OA and glycolysis. Modulating glycolytic metabolism as a possible treatment in KOA may result from targeting glycolysis, particularly glucose transporters and regulatory enzymes [100].

7.1.6. Glucose transporter 1 (GLUT1)

Glucose is required for glycosaminoglycan production and energy in chondrocytes. Chondrocyte absorption, the generation of reactive oxygen species, and cartilage degradation can all be attributed to high glucose levels. In hypoxic environments, the gene of glucose transporter1 (GLUT1) is activated, which contributes to regulating glucose levels. Injuries from OA exacerbate cytopenia and proteoglycan loss in articular cartilage that lacks GLUT1. Increased GLUT1 expression could contribute to the development of OA treatment [101, 102, 103].

7.1.7. Hexokinase 2 (HK2)

The essential glucose metabolism regulator HK2 induces the switch from oxidative phosphorylation to aerobic glycolysis [104]. Its higher-than-normal expression in OA synovial tissue (FLS) results in enhanced RNA expression of proinflammatory cytokines [105].

7.1.8. Pyruvate kinase M2 (PKM2)

In OA chondrocytes, pyruvate kinase M2 (PKM2), a rate-limiting enzyme in glycolysis, is increased which reduces ATP synthesis and promotes cell death [106]. PKM2 has been

suggested as a possible therapeutic target while inhibition can stop cell proliferation, induce cell death, and decrease COL21 and SOX9 expression [100].

7.1.9. 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3)

6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) is a key glycolysis stimulator in human tissues that is downregulated in OA cartilage. Overexpression of this factor progresses the glycolytic process, chondrocyte viability, caspase-3 activation, and collagen expression [107].

7.1.10. Lactate dehydrogenase A (LDHA)

Lactate dehydrogenase A (LDHA), a major component in lactate production, disrupts the synovial tissue metabolism, leading to increased lactate secretion and progression of KOA [108]. Hypoxia enhances glycolysis, and IL-1 β induction increases gene expression, suggesting new therapeutic targets [109].

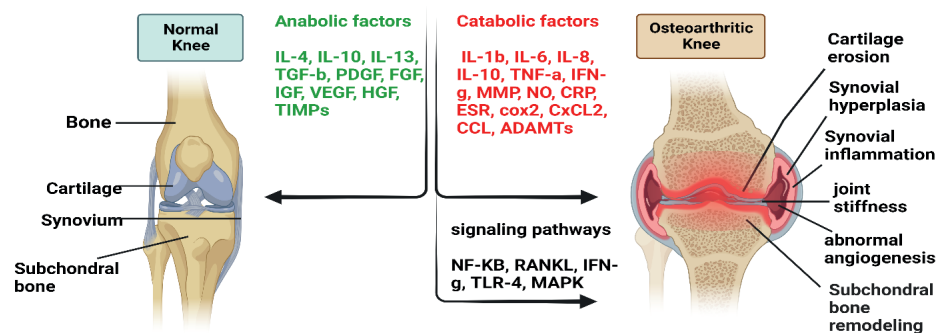


Figure 1: KOA pathophysiology. OA is a degenerative disease that affects cartilage, synovium, the infrapatellar fat pad, and the subchondral bone. It creates osteophytes by causing persistent inflammation, cartilage degradation, and abnormal bone development. Articular cartilage erosion, synovial hyperplasia, angiogenesis abnormalities, joint stiffness, ligament and tendon instability, and aberrant angiogenesis are all symptoms. OA is caused by physiological, molecular, and metabolic changes.

8. Treatment Approaches

8.1. Non-drug treatment

Patients with KOA can control their condition, enhance knee joint function, and delay or modify the pathological process in the early phases. Patients could improve their knee

health through health education, weight loss, and exercise [110, 111]. Losing weight is actually beneficial for reducing knee Pain and stiffness [112]. Muscle strength training successfully decreases the pain and facilitates recovery of knee function [113]. Emotional support is essential for patient guidance [114]. Water sports and Tai Chi a traditional Chinese medicine with therapeutic effects [115, 116]. Physical therapies such as acupuncture [117], ultrasound [118], laser [119], massage [120], spa [121], cupping [122], long-term yoga, and aerobic/strength exercises [123] help to relax tense muscles, enhance blood circulation, and allow inflammatory mediators absorption and discharge. Moreover, a study conducted on patients with OA has shown that a static low-angle squat (SLAS), a novel exercise, has been shown to relieve pain and improve various aspects of mobility and muscle strength as well as knee stability in patients with OA [124].

8.2. Drug treatment

8.2.1. Topical treatment

A clinical trial revealed that the topical drug Lax-T (loxoprofen sodium hydrogel transdermal patch), a non-steroid anti-inflammatory drug (NSAIDs), has the same efficacy and safety as its oral counterpart [125]. Ibuprofen gels and creams [126], topical administration of 2% sodium diclofenac [127], piroxicam [128], natural functional oils [129], quercetin [130], and *Phyllanthus amarus* Schumach [131] are the other relatively effective drugs that are used topically.

8.2.2. Oral treatment

As first-line therapies for KOA, the European Association for Osteoporosis and Economic Areas of Osteoarthritis (ESCEO) recommends glucosamine sulfate and chondroitin sulfate. When combined with undenatured type II collagen supplements, they have demonstrated high effectiveness and tolerability [132, 133, 134]. Although NSAIDs are essential for OA therapy, they can cause gastrointestinal damage [135]. Diacerein, an IL-1 inhibitor, can enhance joint function, delay disease development, alleviate pain, and boost the quality of life [136]. Treatments based on traditional Chinese medicine, such as Duhuo Jisheng decoction, can also be valuable [137].

8.2.3. Surgical treatment

KOA is treated with invasive treatments such as intraarticular puncture and knee joint injection. Glucocorticoids, ozone, hyaluronic acid, platelet-rich plasma, and mesenchymal stem cells are all widely used injectable medications [138, 139, 140, 141]. In KOA patients, glucocorticoids alleviate pain, whereas ozone relieves pain and improves function [142]. Transplanted mesenchymal stem cells are useful in cartilage regeneration and tissue engineering. Early transplantation may result in improved long-term outcomes [143]. Knee Arthroscopy is beneficial in early and middle-stage KOA, with knee arthroscopic loose lobectomy compared to conservative treatment [144]. Inlay plasty utilizes autografts to restore damaged cartilage, whereas microfracture uses pluripotent stromal cells to repair cartilage abnormalities [145, 146]. High tibia osteotomy (HTO) is a surgical method that readjusts the load-bearing line within the coronal plane to shift load-bearing lines from the arthritic chamber to a healthy chamber. It can give long-term survival for certain patients, but patients' age, gender, and OA severity should all be taken into account [147]. Proximal fibular osteotomy (PFO) is a straightforward and successful treatment for medial septal OA, with higher distal displacement indicating a wider range of motion in the tibial fibula joint and more significant relief in OA symptoms [148]. Distal femur osteotomy (DFO) is a well-known therapy for femoral deformities and accompanying symptoms, with a 99-month average follow-up and a 113-month survival rate [149]. Univentricular knee arthroplasty is a long-term and successful treatment option for end-stage single-compartment KOA, significantly lowering postoperative discomfort and complications [150]. Total knee arthroplasty (TKA) is a novel treatment option for knee disorders, with a service life of 15–20 years on average [151].

9. New Treatment Approaches

Disease-modifying OA drugs (DMOADs) may suggest novel targets for repairing the quality and function of OA-affected tissues. DMOADs are categorized into bone-active drugs such as Strontium ranelate which positively improves functional capacity and lowers morphological markers and joint deterioration, and Zoledronic acid [152].

9.1. Immunotherapy

9.1.1. Monoclonal antibodies

Compared to small molecules, monoclonal antibodies exhibit target selectivity and less toxicity in KOA, and have demonstrated promising effects in mouse models and in vitro investigations (Table 1) [153, 154].

9.1.2. Monoclonal antibodies targeting ADAMTS-5

Cartilage loss is a common symptom of OA, caused mostly by proteolysis of structural components such as aggrecan and collagens. Aggrecanases are ADAMTS family enzymes that are involved in cartilage-specific proteoglycans. Researchers have focused their efforts on discovering disease causes while developing novel treatments. A recent research demonstrated that inhibiting ADAMTS-5 is more effective than other types of ADAMTS in human cartilage explants [155, 156]. Besides, a recent study introduced Anti-ADAMTS-5 Nanobody® (M6495) as a novel strategy in the treatment of KOA. M6495 is a 28.1 kDa bifunctional nano body that binds ADAMTS-5 but not ADAMTS-1, -4, or -15 and inhibits its enzymatic activity [157]. M6495 was reported to reduce huARGS, exAGNxl, and GAG following pro-inflammatory stimulation, as well as C2M in HEX. M6495 also inhibited ADAMTS-5-mediated cartilage degradation and total cartilage degeneration, indicating cartilage protection [158].

9.1.3. Monoclonal antibodies targeting interleukin-1 (IL-1)

In OA patients, the cytokines IL-1 and IL-1 play an important part in the disease's etiology. They stimulate MMPs, prostanoids, nitric oxide, and free radicals, inhibit collagen and proteoglycan production, and degrade cartilage. IL-1 antagonists are effective in OA alleviation of pain. mAbs which target IL-1 could prevent disease progression [155, 159].

9.1.4. Monoclonal antibodies targeting tumor necrosis factor (TNF)- α

In OA, synovial cells and chondrocytes release TNF-, a pro-inflammatory cytokine that causes cartilage matrix breakdown and sensory neuron activation. TNF- inhibition can reduce collagenase, MMPs, and pro-inflammatory mediators in OA cartilage explants, indicating that anti-TNF- treatments could be used as a therapy [155, 160].

9.1.5. Monoclonal antibody targeting vascular endothelial growth factor (VEGF)

Angiogenesis is critical for the development of OA because articular cartilage self-repair is restricted. Treatments aimed at restoring tissue quality vary, however regenerating regions are frequently replaced by bone or fibrocartilage. High-dose VEGF expression in osteoarthritic joints may cause OA development and progression, as well as angiogenesis and innervation, which may cause pain in patients. In recent years, using *in silico* analysis and immune cell suppression, researchers have been looking for biomarkers for disease prevention, diagnosis, and therapy. In a study, single-cell RNA sequencing analysis was used to evaluate the expression distribution of VEGFA, a key immune-related gene, in synovial tissues of patients with OA [161]. VEGFA is a tyrosine kinase glycoprotein that plays an important role in angiogenesis, migration, proliferation, and oviduct development [162]. It is also involved in skeletal development, osteoblasts, and osteoclasts, all of which contribute to the formation of endochondral bone [163]. VEGFA has been related to several different cell types, including progenitor cells, stem cells, osteocytes, osteoblasts, osteoclasts, and mesenchymal stem cells. VEGFA expression levels that are high are linked to several pathways [164, 165]. Therefore, it might be a possible immune-related biomarker for the detection and early treatment of KOA [161].

9.2. Cell-based therapy

9.2.1. Macrophages

In a recent research, the use of artificial M2 macrophages as the promising treatment of disease-modifying OA was considered [180]. M2 macrophages have anti-inflammatory characteristics and stimulate cartilage regeneration, relieving OA in mice. However, controlling their secretion is difficult [181, 182]. An artificial M2 macrophage (AM2M) with a yolk-shell shape was created to improve its therapeutic effectiveness in OA therapy. AM2M binds to inflammatory regions, inhibiting immunological activation, and is believed to disrupt the self-perpetuating OA cycle [180]. Moreover, the novel 99mTc-EC20 imaging technology identifies activated macrophages *in vivo*, giving the first evidence of macrophage involvement in OA. The link between active macrophages and the severity of OA indicates therapeutic targets for symptom and structural change [183].

TABLE 1: Monoclonal antibodies (mAbs) which have been investigated in clinical trials.

mAb	Target/Mechanism of Action	Rout of Administration	Application	Effect(s)	Reference
CRB0017	Ancillary domain of ADAMTS-5 spacer domain of aggrecanase-2	Intra articular injection	STR/ort mouse Rodents (57BL/6J mice)	Modulate a series of proteins like fibromodulin which associates with aggrecanase	[166, 167]
AMG108	Anti-interleukin-1 receptor type 1	SC/IV/ intraarticular	Humanized	No beneficial effects when compared with placebo after a 3-month follow-up	[168, 169]
Lutikizumab (ABT-981)	Anti-interleukin-1 (IL-1) alpha/beta dual variable domain (DVD)	SC	Animal/human	Reduce pain and slow structural progression in OA was generally well tolerated in patients with KOA and engaged relevant tissue targets, eliciting an anti-inflammatory response	[170, 171]
Canakinumab (ACZ885)	Anti the IL-1 β receptor	Intra-articular injection	Human	Increased the proteoglycan levels and decreased NO levels in cells cultured with TNF- α	[172]
Adalimumab	TNF-a	Intra articular injection	Human	Effective and tolerated for moderate to severe KOA	[173]
Infliximab (chimeric bivalent mAb)	TNF-a	Intra-articular injection	Human/murine	Reduce cartilage degeneration and reducing TNF- α and nitric oxide (NO) in the synovial fluid	[174, 175]
Tanezumab (RN624)	Anti-NGF	IV	Human	Relieves hip and knee pain in individuals with OA, improvement in function, with mild and moderate adverse events	[176]
Fulranumab (AMG 403)	Anti-NGF	SC	Human	Significant efficacy in pain measures and physical function	[177]
Bevacizumab	Anti-VEGF antibody	SC	Rabbit	repaired articular cartilage in rabbit KOA model	[178]
GSK3858279	Anti-CCL17 monoclonal antibodies	SC	Human mab	reduces pain and joint disease in murine arthritis	[179]

mAb: monoclonal antibody, SC: subcutaneous, IV: intraventricular

9.2.2. Stem cell therapy

Stem cell therapy seems to be a promising, reliable, and curative approach to treating degenerative diseases, including OA due to its regenerative properties and ability

to differentiate into more than 200 cell types [184]. Stem cells have been widely investigated for treatments of OA. In recent years mesenchymal stromal cells have been at the center of attention [185]. The capacity of mesenchymal stem cells (MSCs) to develop into osteoblasts and chondrocytes along a mesodermal lineage has revealed that they have a fundamental role in tissue repair and regeneration. However, it is more possible, that MSCs alter the local environment associated with OA via paracrine signaling rather than direct differentiation, leading to disease modification [186].

9.2.3. Adipose-derived mesenchymal stromal cells (ADSCs)

Autologous ADSCs originate in adipose tissue and release growth factors, cytokines, chemokines, and exosomes [187, 188]. These might have an impact on progenitor cells and the microenvironment, activating repair mechanisms and reversing degenerative processes. ADSCs are increasingly being employed to treat musculoskeletal disorders, particularly those that are degenerative [189, 190, 191]. Autologous ADMSC therapy appears to be a safe and effective therapy for KOA and may have the potential to prevent disease progression [192]. Recent evidence showed that micro fragmentation provides a viable alternative to cell expansion and enzymatic breakdown of adipose tissue for the treatment of KOA [193]. Besides, mechanically isolated autologous adipose tissue-derived stromal vascular fraction (SVF) origination from adipose tissue is optimal for treating KOA. Also, it might be a practical therapy option for those with degenerative OA [194].

9.2.4. Bone marrow-derived mesenchymal stem cell therapy (BM-SCs)

A clinical trial study reported that a single intraarticular injection of expanded autologous BM-MSCs in vitro contributes to long-term clinical and functional improvement of KOA [195]. A novel strategy for the treatment of KOA is biomaterial-based mesenchymal stromal cell-based treatment, which makes use of 3D printing and natural and synthetic materials such as collagen, alginate, hyaluronic acid and polyethylene glycol, polylactide acid, and polyurethane science technology and provides promising options for cartilage formation and functional repair [1].

9.2.5. Synovium-derived mesenchymal stem cell therapy (Sy-MSCs)

Sy-MSCs, which are generated from the synovial membrane, promote regeneration via paracrine signaling, direct cell-cell contacts, and extracellular vehicles. They are more

chondrogenic than other sources of mesenchymal stromal cells. Sy-MSCs, which are high in collagen III, V, and VI, express CD-68, CD-14, and adhesion molecules such as CD-44 and VCAM-1. As a result, they may be useful in managing cartilage loss in OA [196, 197].

9.2.6. Human umbilical cord mesenchymal stem cells (hUC-MSCs)

hUC-MSCs not only have normal stem cell biological properties, but they also have abundant sources and easy material extraction. Therefore, they are useful to use in treating OA, promoting articular cartilage generation, and secreting cytokines for inflammatory immune regulation. hUC-MSCs are more capable of proliferation, differentiation, and immunological control than other types of stem cells. Furthermore, there are no ethical concerns related to their use. The majority of people recover within 24 hours after receiving the injection. hUC-MSCs have the potential to reduce pain, improve knee joint function, and potentially delay the need for surgical intervention in both non-surgical and other situations, making them well-suited for clinical promotion and application [184]. According to a study, Patients undergoing treatment of KOA with hUC-MSCs might be expected to experience improvements in clinical outcomes [197, 198].

9.3. Exosome therapy

Exosomes, small extracellular vesicles produced by numerous cells, are promising options for OA treatment because of their biocompatibility, immunomodulatory capabilities, and specific targeting of cells and tissues [199, 200]. Exosomes can be derived from individual cells, reducing the possibility of immunogenic reactions. They have shown promise in improving cartilage regeneration, reducing inflammation, and relieving chronic pain in OA patients. Exosome-based therapy has proven greater effectiveness and safety in the treatment of OA [8, 201]. These small molecules cover medicinal compounds such as anti-inflammatory drugs, growth factors, and microRNAs, which are released with specificity and effectiveness so they could be effectively used as promising vehicles in drug delivery systems (DDSs) for OA therapy [200, 202]. In this line, according to one study, Curcumin-treated MSC exosomes restore down-regulated miR-143 and miR-124 expression, increase NF-kB and ROCK1 expression, and delay OA development. Indeed, the 3'UTRs of NF-kB and ROCK1 were demonstrated to contain the binding sites for miR-143 and miR-124, respectively [203]. Besides, bone morphogenetic proteins-7 (BMP-7) modified synovial mesenchymal stem cells-derived exosomes (SMSCs-exo) therapy increased LPS-induced macrophage and chondrocyte

proliferation and decreased inflammation and ameliorated KOA via boosting M2 polarization in vitro and in vivo [204]. Exosomes carry miRNA, including miR-1, miR-133a, miR-133b, miR-206, and miR-486 [205]. MiR-206 is crucial for OA development by affecting apoptosis and autophagy of articular chondrocytes. Exosomal miR-206 from BMSCs may regulate osteoblast differentiation by reducing E1f3 expression, a factor that has been demonstrated to induce cartilage degradation in a model of post-traumatic OA. Therefore, it might be effective as a therapeutic approach (Table 2) [206].

TABLE 2: Mesenchymal stem cells derived exosomes in knee osteoarthritis (KOA) treatment.

Exosome	Target Cells	Mechanisms of Action	Biological Effects on KOA	References
Plt-exo	Chondrocyte	Restore the decreased collagen II expression and block cartilage matrix breakdown / modulate immune responses and inflammatory reactions / mediate cell-to-cell cooperation / contribute to the transduction of intracellular signaling	Attenuate cartilage degeneration and subchondral bone loss	[207]
BM-MSCs-exo	Primary human chondrocytes	Exosomal MEG3 inhibited IL-1 β -induced senescence and apoptosis in chondrocytes.	Reducing the senescence and apoptosis of chondrocytes	[208]
Sy-MSCs-exo	Chondrocytes	Increase the expression of catabolic genes	Chondrogenic effect and repair the articular cartilage	[209]
ADSCs-exo	Osteoarthritic cartilage	Promote cartilage repair and inhibit inflammation	Repair cartilage damage and treat OA	[210]
hUC-MSC-exo	Chondrocyte	Promoting chondrocyte proliferation and migration and inhibiting chondrocyte apoptosis	Chondrogenic effect and treat OA	[211]

Plt: platelet, exo: exosome, BM-MSC: bone marrow mesenchymal stem cell, Sy-MSCs: synovial fluid-derived mesenchymal stem cell, ADSCs: adipose tissue-derived mesenchymal stem cell, hUC-MSCs: human umbilical cord mesenchymal stem cell

9.4. Gene therapy

Gene therapy approaches attempt to decrease the degeneration and increase the repair and regeneration of afflicted areas by controlling genes with DNA, RNA, and short oligonucleotides [212]. Several studies have indicated that miRNA-140 intra-articular injections have an anti-inflammatory impact and decrease the course of OA [213]. MicroRNA levels such as miRNA-181a-5p in osteoarthritic cartilage are elevated. Anti-sense oligonucleotide therapies might have the potential to affect important cellular pathways and alter disease development in preclinical in vivo models [214, 215]. In animal models, intra-articular gene therapy is being investigated for the treatment of

OA. Several cDNAs have shown therapeutic efficacy, including cytokines, cytokine antagonists, enzymes, and growth factors. Human clinical trials have also set in with six gene therapies in development [216].

9.5. Autologous platelet-rich plasma (PRP) and platelet lysate (PL)

Autologous PRP is a supra-physiological concentration of platelets that is known as an autogenous source of several fundamental growth factors including platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), transforming growth factor-beta (TGF- β), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF) [217, 218]. Indeed, because of their ease of preparation, access to higher concentrations of platelet-related growth factors compared to baseline blood, and efficacy in inducing articular tissue anabolism and improving joint function, platelet-derived products have fueled an enormous body of research aimed at therapeutic applications of PRP and PL in various fields of bone disorders, such as muscular injuries, joint degeneration, orthopedic surgery, and bone fractures [219]. Because of the significantly larger concentrations of growth mediators, notably PDGF and TGF- β , which have beneficial effects on the improvement of the healing cascade, there has recently been an increasing interest in using PL instead of PRP. As a result, PL could be a useful replacement candidate for PRP in the treatment of articular cartilage lesions [220, 221]. Besides, platelet-rich plasma is more effective than hyaluronic acid and is still used as a second-line therapy [222, 223].

9.6. Other treatment approaches

9.6.1. Genetically modified MSCs (engineered MSCs)

MSCs have poor in vivo efficacy due to poor survival, retention, and engraftment. They require genetic alteration utilizing viral vectors including retrovirus, lentivirus, baculovirus, and adenovirus to increase survival, migration, and growth factor secretion. These vectors enhance MSC homing to defects or inflammatory locations. Although preclinical investigations have shown efficacy, clinical trials have yet to be done [197, 224].

9.6.2. Engineering hyaluronic acid

The development of injectable therapies that restore the viscoelastic qualities of deteriorated synovial fluid indicates the physicochemical significance of hyaluronic acid (HA) a vital component of synovial fluid and cartilage in joint lubrication. Tissue engineering techniques are used to boost joint retention and controlled medication release. To deliver cells and biomolecules to OA joints, hydrogels are constructed out of HA [225, 226].

9.6.3. SM04690, a Wnt inhibitor

SM04690, a Wnt signaling inhibitor, has been investigated for the treatment of OA, with clinical studies demonstrating its safety, effectiveness, decreased pain, and enhanced functionality [227].

9.6.4. UBX101 (Senolytic)

UBX101, a senescence-targeting drug, has been demonstrated to be beneficial in treating OA in mice. It suppresses the tumor suppressor gene p53 and causes death in senescent cells, requiring clinical investigations to assess its safety and tolerability [228, 229, 230].

9.6.5. Transient receptor potential vanilloid 4

Because TRPV4 ion channels are important in chondrocytes, local injection of a transient receptor potential vanilloid 4 (TRPV4) agonist as a possible therapy for OA appears interesting [231].

9.6.6. Neural epidermal growth factor-like 1 (EGFL-like 1)

Nell-1-deficient mice have a rapid progression and aggravation of OA, indicating that neural EGFL-like 1 (NELL-1) might be used as a modifying medication with pro-chondrogenic and anti-inflammatory properties [232].

9.6.7. TPCA-1 (a κ B kinase inhibitor) and tofacitinib (a Janus kinase inhibitor)

Tofacitinib and TPCA-1 could maintain cartilage extracellular matrix (ECM) during inflammation, potentially modulating the inflammation-driven OA [233].

9.6.8. Lorecivivint

Lorecivivint, a Wnt signaling pathway modulator, has been demonstrated to be safe and well-tolerated for intraarticular injections in KOA patients [234].

9.6.9. Quercitrin

It has been demonstrated that quercitrin exhibits anti-osteoarthritic characteristics by postponing ECM degradation, making it a promising option for the treatment of early OA [235].

9.6.10. Microparticles

Due to their small size, microparticles can be injected into joints and can release the medications that are loaded inside of them while being retained within the joint [236].

9.6.11. Nanoparticles

As drug delivery systems, polymeric, micelle, and liposomal nanoparticles can penetrate cartilage and increase the period that medication is retained there. According to studies, rapamycin-loaded micelles in gelatin hydrogels prevent the progression of the disease, while PEGylated kartogenin-based micelles in HA hydrogels do the opposite [237, 238, 239, 240].

9.6.12. Hydrogels

Hydrogels, such as the HA-doxycycline hydrogel, may decrease osteophyte development and cartilage fibrillation in the treatment of OA. However, rapid-solidification hydrogels are preferred because they are less likely to produce extrusion or fragmentation. They also act as tissue healing scaffolds [241, 242, 243].

9.7. Bone marrow aspirate concentrate (BMAC) injections

Bone marrow acquired via iliac crest aspiration is a rich source for extracting mesenchymal stem cells, other progenitor cells, and related cytokine/growth factors. Recent studies have indicated to remarkable results with the use of bone marrow aspirate concentrate (BMAC) for pain alleviation in the treatment of localized KOA [244]. A study demonstrated the efficacy of bone marrow aspirate concentrate (BMAC) injections as a non-surgical therapy for KOA pain. A 65-year-old man was treated with (BMAC) injections for arthritis-related knee discomfort. His physical condition improved by 90% and his discomfort was significantly reduced after a 3-week treatment [245].

9.8. Autologous chondrocyte (CH) transplantation

Autologous chondrocyte (CH) transplantation is a novel strategy to treat post-traumatic OA (PTOA). A study showed that when original CHs were co-cultured with degenerated CHs, apoptosis, collagen X, IL-6, and TNF- were elevated, whereas collagen II and IL-10 were decreased compared to the separated culture condition. Transplanting the IL-10-overexpressed CHs in PTOA patients would be consistent and effective in alleviating CH degeneration [246].

10. Conclusion

KOA is the most common type of arthritis, causing a great deal of pain and disability for people as well as a significant financial burden on the healthcare system. Nonetheless, no definitive cure for this condition has been developed, new breakthroughs in the discovery of new techniques in collaboration with other biological sciences point to the possibility of finding effective alternatives to KOA treatment in the near future.

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