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Review

Osteoarthritic knee: Advances in Epidemiology, Emerging Etiopathologies and Adipose-Derived Stem Cells-based Therapies

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ABSTRACT: Knee osteoarthritis (KOA) is a degenerative disorder that affects the joint in a non-uniform and focal manner. It is characterized by the loss of hyaline articular cartilage, along with bony remodeling, capsular stretching, and weakness of periarticular muscles. It could be ascribed to etiological factors that are modifiable (obesity, joint injury, occupational hazards, physical inactivity), non-modifiable (age, female gender, and genetic predisposition, racial/ethnic differences), or emerging, such as high blood pressure, vitamin D deficiency, and metabolic syndrome, which might contribute to KOA pathophysiology. KOA treatment is multimodal, and recent years have witnessed a shift from primarily pharmacologic, surgical to regenerative therapies ones, due to limited advantages of the former and evidence that advanced approaches are more likely to suppress pathological symptoms in the long term and to delay or prevent functional decline. Minimally invasive stem cell-based alternatives such as adipose-derived stem cells (ADSCs) are being explored owing to their differentiation potential towards chondro-, osteo-, and adipogenic lineages for osteochondral reparative regeneration. ADSC-derived extracellular vesicles, particularly exosomes (ADSC-exo), are gaining prominence in the treatment of KOA due to their unique regenerative and anti-inflammatory properties. These exosomes offer several advantages compared to cellular interventions, being a cell-free therapeutic strategy, low immunogenicity, and potential to deliver bioactive molecules, promote anti-inflammatory effects, and cartilage repair and regeneration. ADSC-exo expresses miRNA and improved safety by regulating various pathways such as PI3K/AKT/mTOR signaling or Wnt/β-catenin signalling. Combinatorial approaches have also been applied with ADSCs, such as platelet-rich plasma, shockwave therapy, xanthan gum, hyperbaric oxygenation, and nanoparticles, which have shown significant improvements in alleviating KOA. Based on the above evidence, we have reviewed the advances in epidemiology, emerging etiopathologies, and ADSCs-based revitalization strategies for the osteoarthritic knee joint.

Keywords: Knee osteoarthritis, Adipose-derived stem cells, Exosomes, Chondrocyte

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1. Introduction

Knee osteoarthritis (KOA) is a major musculoskeletal disorder that develops primarily due to cartilage degeneration [1, 2]. In addition, synovial and systemic inflammation, meniscal and extracellular matrix degeneration, osteophyte formation, ligament loss, joint hypertrophy, systemic inflammation, bone remodeling, extracellular matrix (ECM) degradation, chondrocyte apoptosis, and subchondral bone thickening are some other featured characteristics of KOA progression [3-5]. Alterations in the bursa, periarticular muscles, fat pads, and nerves could also be attributed to KOA [4]. The risk of KOA is much higher among females than males, with the most common etiological factors such as age, heredity, knee surgery and injury, obesity, excessive exercise, lifting, and bending [6, 7]. KOA severely affects mobility and significantly lowers the quality of life (QoL), specifically in the aging population. The incidences of KOA vary from 10.0 to 50.0% depending upon age and type of KOA, i.e., symptomatic or radiographic [8]. It has been estimated that the cases of KOA have approximately doubled and tripled in women and men, respectively, over 20 years [8, 9], which portends an extreme socioeconomic burden on society.

Treatment of KOA becomes challenging due to the low regenerative potential of knee cartilage and the complex pathophysiological changes during disease progression [5]. The current therapeutic interventions, such as surgery, therapeutic medicines, weight reduction, and exercise, help to lower inflammation and pain [10]. Notably, traditional medicines also gained renewed interest due to their therapeutic potential for KOA. To date, modern therapies are only effective in providing symptomatic relief. Alternatively, recent studies have demonstrated the therapeutic potential of stem cells, exosomes, platelet-rich plasma (PRP), and a stromal vascular fraction (SVF) as a regenerative therapy for the treatment of various incurable disorders [11-13]. Both cell-mediated (stem, progenitor cells, or colony-forming unit) and cell-free (extracellular vesicles and exosomes) induce various cellular and molecular changes to regenerate injured/damaged tissues. Concurrently, the structural modification potential of regenerative medicine could be an effective way to promote the healing of injured cartilage [14]. These regenerative agents inhibit inflammation, lower pain, and improve the range of motion in the joints [6]. Furthermore, immunosuppressive and immunoregulatory properties also contribute to the therapeutic value [15, 16]. The paracrine effect of stem cells further promotes the generation of chondrocytes and neo-cartilage tissues.

Among the stem cells, adult mesenchymal stem cells (MSCs) are preferred over embryonic stem cells due to ease of harvest and no ethical concerns. Moreover, the therapeutic potential of MSCs is attributed to their ability to differentiate into chondrocytes, osteocytes, adipocytes, myocytes, and other lineages [17]. MSCs have been extracted from tissue such as adipose, bone marrow, dental pulp, umbilical cord blood (UCB), amniotic fluid-derived, peripheral blood, endometrium, skin, skeletal muscle, synovium, and synovial fluid [15, 18]. Of the above sources, bone marrow-derived stem cells (BMSCs) and adipose tissue-derived stem cells (ADSCs) are among the most used stem cells for regenerative therapies [17]. However, ADSCs are the favored owing to their minimally invasive nature, ease of harvest [19, 20], superior proliferation and differentiation [17, 21]. Further, the higher stem cell yields with improved safety and efficacy from the adipose tissues compared to bone marrow makes it more advantageous [19]. Thus, considering the superior therapeutic potential of ADSCs, we critically evaluated and discussed the therapeutic aspects of ADSCs and their secretome in treating KOA.

2. Epidemiology and Etiopathogenesis

A recent meta-analysis of 88 studies with 10,081,952 participants reported global KOA prevalence of 16.0% in individuals aged 15 and over, which increased to 22.9% in those aged 40 and older [8]. This study also estimated global KOA incidence at 203/10,000 person-years, with limited data outside Europe and North America. In the U.K. and USA, the incidence is 315/10,000 person-years, and 130/10,000 person-years, respectively. To date, approximately 37% of individuals over 50 years of age in Taiwan experience OA [22], with a significantly higher prevalence among women compared to men.

KOA is a prominent reason for restricted mobility among the aged population [23]. Its severity is primarily determined by the radiography-based Kellgren–Lawrence (KL) system [24]. Based on the pathological features, the KL system groups KOA into the following grades: (i) grade 0 (non-pathological), (ii) grade I (possibility of narrow joint space and osteophytic lipping) (iii) grade II (joint space narrowing and osteophytic lipping) (iv) grade III (moderate multiple osteophytes, definite narrowing of joint space, sclerosis, and possible deformity of bony ends) (v) grade IV (large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends)[25, 26].

Recent decades have witnessed significantly increased incidences of KOA due to high exposure to etiopathological risk factors (Figure 1) [23], which could be categorized into modifiable, non-modifiable, and emerging. Idiopathic KOA is mainly associated with non-traumatic risk factors such as increased body mass index (BMI), obesity, gender (female), age, genetic

susceptibility, congenital abnormalities, hormonal changes, and metabolic disorders [27-29], whereas non-idiopathic KOA is mainly associated with the history of a previous knee injury. The risk of injury in the knee joint is high in case of dislocation, derangement, fracture, and sprain, while low in soft-tissue injury [30]. The risk factors for KOA can be divided into non-modifiable, modifiable, and emerging, which have been discussed in the next sections.

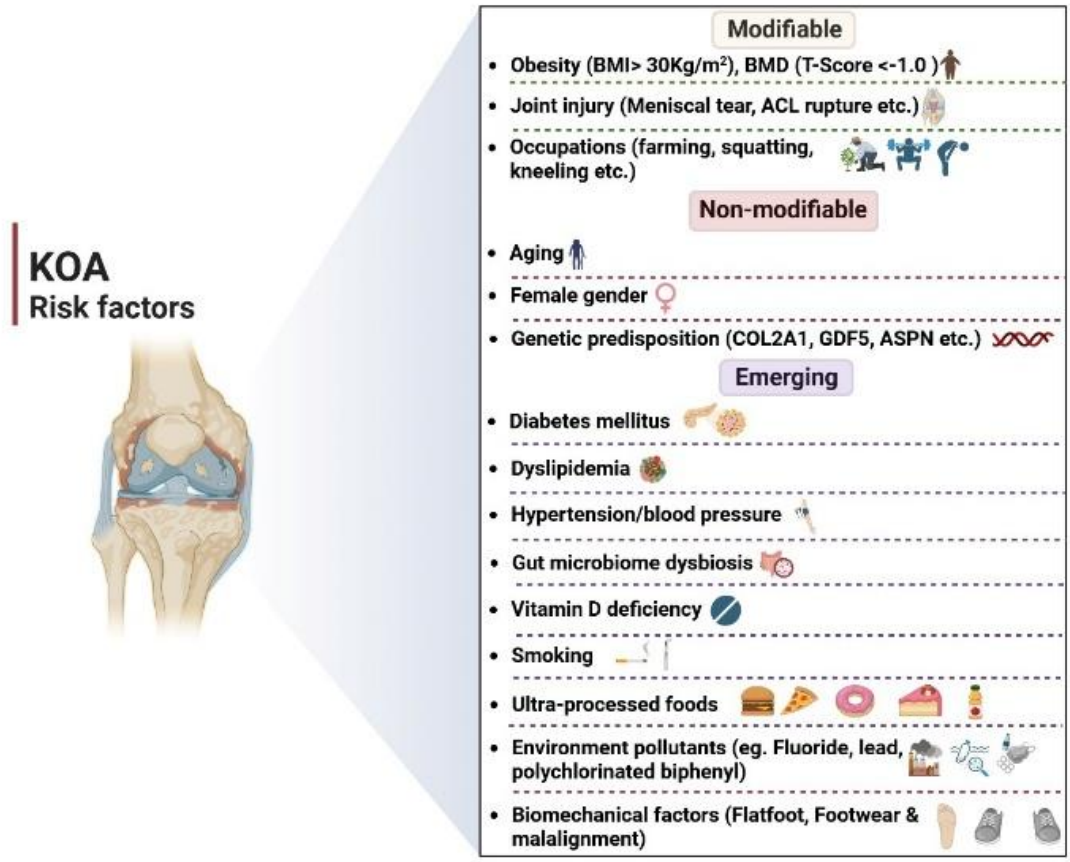

Figure 1. Risk factors for KOA, categorized as modifiable, non-modifiable, and emerging. BMI: Bone mass index, ACL: Anterior cruciate ligament. Created in BioRender. Dubey, N. (2025) https://BioRender.com/bdx9put.

3. Non-modifiable risk factors

3.1 Aging

Aging is an intricate process characterized by the cumulative impact of various molecular and cellular damage over time. This results in a gradual decline in physical and mental capabilities and may contribute to KOA pathophysiology. In a study including over 30.000 participants (over 20 years) reported increased KOA risk in adults with accelerated biological aging, specifically among females and older adults [31]. A systematic review and meta-analysis of the elderly Indian population (n=5,029, aged ≥ 60 years) found a doubled risk of KOA among females (50.7%, 95% CI: 33.3%-67.9%) compared to males (26.2%, 95% CI: 10.5%-45.7%) [32]; whereas in another meta-analysis, age ≥40 has been reported as a risk factor for KOA [33].

3.2 Gender

Studies have also evaluated sex-specific KOA risk, which is generally higher in women [34], with a greater difference after age 40, which could be due to differences in joint anatomy, alignment, hormonal influences, muscle strength, obesity, or genetics [35]. A multicenter osteoarthritis study investigated gender-based differences in knee pain and found higher VAS in women than men, regardless of KL grade. These differences were increased in patellofemoral OA (PFOA)[36].

3.3 Genetic predisposition

KOA is a multifactorial disease with several involved genetic factors. GDF5, also known as cartilage-derived morphogenetic protein 1 (CDMP1) and BMP-14, is an extracellular signaling molecule that plays a key role in

the development, maintenance, and repair of bone, cartilage, and other tissues of the synovial joint [37]. A systematic review and meta-analysis examined the association between GDF5 rs143383 single-nucleotide polymorphism (SNP) and OA susceptibility and found a more significant association in Caucasians. However, GDF5 core promoter polymorphism has also not been found to be associated with KOA in the Korean [38] and Greek [39] populations. The COL2A1 gene polymorphism with advanced stages of KOA has also been reported in the Mexican Mestizo population [40]. In this line, the asporin (ASPN) gene encoding a protein of the extracellular cartilage matrix, which contains a triplet repeat encoding for aspartic acid (D), was found to be associated with KOA in a case-control Japanese study [41]. Specifically, the D15 allele could be considered a risk for KOA in the Japanese population.

Further, genome-wide association studies (GWAS) have also recognized more than 100 genetic loci associated with KOA. These genetic variants could help in predicting individual genetic OA risk by using polygenic risk scores (PRS) that aggregate the effects of common SNPs. In a meta-analysis, a population-based cohort of 12,732 individuals from the Rotterdam Study, the PRS-derived from knee-specific GWAS found odds ratios (OR) per standard deviation (SD) 1.6 of 1.6 for total knee replacement [42]. PRS-based on multi-trait analysis of GWAS (MTAG) in 2,852 Japanese individuals (1,776 women and 1,076 men), showed OR per SD increase of 1.24 [43]. This evidence implies that PRS could play a key role in OA prevention.

4. Modifiable risk factors

4.1 Obesity

Obesity [body mass index (BMI) > 30 kg/m^2] and overweight (BMI > 25 kg/m^2) have been identified as major risk factors for the KOA development [44]. Higher BMI level is associated with increased pain scores, reduced physical activity, and disability. Mechanistically, elevated BMI intensifies the pressure load on the joint's tibial plateau, and these pathologic alterations in KOA may lead to the occurrence of subchondral bone remodeling, especially in advanced OA manifested by an abnormally high bone mineral density (BMD) phenomenon [45]. This implies that the effect of high BMI on the pathological process of KOA might be limited to articular cartilage damage, but also to abnormal subchondral bone remodeling, which is osteochondral injury to the whole joint. In the activated adipose tissues, the level of pro-inflammatory cytokines such as IL-6, IL-1, IL-8, TNF-α, and IL-18 remains elevated with reduced regulatory IL-10 [46, 47]. The leptin gene linked to obesity might also contribute to the KOA progression. The abnormal mechanical/occupational leading results in altered matrix metalloprotease (MMP)-1, collagen fiber orientation, chondrocyte metabolism, and proteoglycan production, leading to the development of post-injury KOA. Consequently, the increasing incidence of obesity has a significant impact on the high prevalence of KOA [23, 48].

Further, as bone is considered an integral structure in the OA pathogenesis, the interrelationship between BMI and bone mineral density (BMD) is plausible. Interestingly, in a recent study, a low BMD level has been reported in severe KOA (attrition) [49]. The preponderance of evidence also indicates that greater systemic BMD is associated specifically with an osteophyte-predominant hypertrophic phenotype of radiographic KOA [50].

4.2 Joint injury

The anterior cruciate ligament (ACL) injury triggers structural, biological, neuromuscular, and mechanical changes leading to loss of joint mechanoreceptors, impaired muscle function, proprioception loss of dynamic stabilizers, damage to static stabilizing structure, joint derangement, damage to cartilage, and meniscus, along with elevated level of oxygen free radicals, inflammatory cytokines, matrix degradative enzymes [51].

4.3 Occupation

Occupations demanding heavy physical stress and load may be a risk factor for KOA. In a systematic review and meta-analysis of observational studies, the occupations involving kneeling, squatting, heavy lifting, frequent climbing, and standing have been found to increase the odds of KOA [52]. A case-control German study revealed kneeling/squatting occupational risk factors for KOA in women [OR: 2.52 (>8,934 hours/life)] and men [OR: 2.16 (12,244 hours/life)] [53]. Taken together, work-related factors are crucial in assessing the KOA risk and in deriving preventive measures.

5. Emerging risk factors for KOA

5.1 Diabetes mellitus (DM)

Our recent study demonstrated that DM may be independently associated with KOA development through a glycation-mediated inflammatory cascade [54], and obesity may not be a confounding factor [55]. The elevated joint pain in diabetic patients with KOA could be attributed to increased synovitis, synovial immune cell infiltration, and erythrocyte extravasation [56]. It has also

been concluded from the osteoarthritis initiative data that DM could be a risk factor for increased pain with worse physical and mental health status, in addition to and independent of higher BMI and radiographic OA severity [57].

5.2 Dyslipidemia

Hyperlipidemia typically includes elevated levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C), and these indices have been observed to be higher in patients with radiographic KOA [58]. In a nationwide South Korean cohort, dyslipidemia was associated with an increased risk of KOA regardless of obesity [59]. The increased levels of LDL could activate the synovial inflammation and accelerate ectopic bone synthesis [60]. The oxidized LDL may accelerate cartilage destruction and inflammatory chondrocyte apoptosis in OA by disrupting the transcription factor EB (TFEB)-regulated autophagy-lysosome pathway [61].

5.3 Hypertension/Blood pressure

Recent research is gaining attention in the relationship between hypertension and KOA, possibly due to blood flow-controlled bone vascular function and osteogenesis [60]. In a recent study, using the whole-organ magnetic resonance imaging score, Ashmik et al. graded structural knee abnormalities and showed that the diastolic blood pressure might also be associated with greater increases in cartilage T2 parameters over 48 months, signifying accelerated cartilage degeneration [62]. A systematic review and meta-analysis including 26 studies with 97,960 participants revealed significantly increased KOA in the hypertension group (OR = 1.62, 95%CI = 1.32-1.98) [63]. A stronger association of hypertension with radiographic KOA (OR = 1.89, 95%CI = 1.40-2.54) was found than with symptomatic KOA (OR = 1.39, 95%CI = 1.17-1.65). This was statistically significant for the studies that adjusted for body mass index (BMI) (OR = 1.42, 95%CI = 1.13-1.78), and was particularly strong in women (OR = 2.27, 95%CI = 1.17-4.39)

5.4 Gut microbiome dysbiosis

Interestingly, gut microbiome dysbiosis may also contribute to KOA by exacerbating systemic inflammation and pain syndromes. Specifically, a greater abundance of Streptococcus spp. may be associated with KOA pain [64]. It is hypothesized that this could be mediated via induction or exacerbation of local joint inflammation by metabolites produced by Streptococcus spp. in the gastrointestinal tract. A systematic review also evidenced altered gut microbiome and joint microbiome in patients with KOA versus controls, where increased levels of lipopolysaccharide and lipopolysaccharide-binding protein in synovial fluid were found and were associated with activated macrophages [65]. This was correlated with joint space narrowing, worsened osteophyte severity, and pain scores in KOA patients, possibly via the microbiota-inflammaging-OA axis as a promising line of investigation [66]. Although the joint space is considered to be sterile, recent evidence implies that microfractures in the osteochondral junction in osteoarthritic joints can cause blood vessels to transport and translocate factors present in the bloodstream to overlying cartilage in the joint space [67-69]. The above scientific literature implies the involvement of gut microbiome dysbiosis and KOA.

5.5 Vitamin D

Higher vitamin D deficiency has been associated with increased KOA risk and severity. An analysis of the Osteoarthritis Initiative database revealed that increased vitamin D is associated with reduced WOMAC pain scores in males [70]. Since vitamin D plays a crucial role in calcium absorption and bone health, its insufficiency may significantly impact bone-joint health and pain perception in males, who have higher bone density and muscle mass. This underscores a potential sex-specific therapeutic approach for KOA males. In a systematic review and meta-analysis including 13 studies, a significantly reduced vitamin D level of −8.68 (95 % CI, −12.21 to −5.51, $p < 0.00001$, $I2 = 82$ %) was observed in the Indian population with 1503 KOA cases [71]. It was also reduced in other Asian populations with 497 KOA [−18.36 (95 % CI, −34.72 to −2.00, $p < 0.00001$, $I2 = 100$ %)]. Interestingly, in the Wistar male rats with anterior cruciate ligament transection combined with medial meniscectomy-induced KOA, vitamin D supplementation exerted chondroprotective impacts by attenuating cartilage matrix (by increasing C-telopeptide of Type II collagen), effectively suppressing OA pain, inflammation (inhibiting IL-1β, TNF-α, and IL-6), and chondrocyte destruction by lowering MMPs levels specifically [72]. This indicates that vitamin D could play a protective role in KOA.

5.6 Smoking

Surprisingly, smoking is also linked with a high prevalence of OA; however, with varying prevalence patterns [73, 74]. An Individual Participant Data (IPD) meta-analysis of radiographic KOA knees with a KL grade 0 or 1 at baseline, totalling 10,072 knees from 5997 participants from three large cohorts i.e., the Osteoarthritis Initiative (OAI), the Multicenter

Osteoarthritis Study (MOST), and the Cohort Hip and Cohort Knee (CHECK) study, concluded that smoking offers no protective effect against KOA [75]. Notwithstanding, smoking in OA male patients accelerates cartilage damage and increases the pain severity [76]. On the contrary, in the KOA progression study, the significant incidence rate of KOA was 41.3%, 26.6%, and 22.9% in the non-smoker, ex-smoker, and smoker groups, respectively (P<0.001) [77]. Also, the incidence rate of knee replacement surgery due to OA was lower among smokers (3.5%), when compared to non-smokers (8.4%) and ex-smokers (3.6%). The conflicting associations between smoking and KOA, acting as a risk factor in some studies while appearing protective in others, could largely be ascribed to methodological variations (cross-sectional versus prospective) and confounding variables (BMI, physical activity, dose-response relationships), and mortality bias. Notwithstanding, these results suggest that smoking portends the likelihood of developing KOA, and thus reducing tobacco intake can be advantageous in reducing KOA incidence.

5.7 Ultra-processed food (UPF)

Increasing evidence suggests that UPFs could be the emerging modifiable environmental accelerator for KOA. These are the processed foods and beverages, with added sugars, saturated and trans fats, chemical additives like artificial sweeteners, dyes, and other chemicals, purposed to extend shelf-life and enhance taste; as a result, their overconsumption and addictive tendencies are induced owing to their hyperpalatability. The data from the Osteoarthritis Initiative have shown that higher UPF consumption is associated with worse knee joint pain, cartilage thickness, and slow gait, particularly in women [78].

Recently, a high UPF diet has been shown to reduce 0.76% muscle mass in the trunk while 1.25% in the appendicular region, particularly in young and middle-aged adult Americans, indicating a detrimental impact of UPF on musculoskeletal health [79]. In a UK Biobank-based cohort of 163,987 participants, consuming UPF revealed a higher risk of KOA, which was suppressed to 6% after replacing 20% of the UPF diet with an equivalent proportion of unprocessed or minimally processed food [80].

5.8 Pollution

Further, pollutants such as lead have been reported as a possible contributor to KOA due to their toxic effects. In a preliminary Egyptian study, the median blood lead level of 6.35 μg/dl has been significantly correlated with KOA severity either clinically or radiologically [81]. This is further supported by the Johnston County Osteoarthritis Project, in which the cross-sectional analysis revealed an association of whole blood lead levels (1.8 μg/dl) with radiographic and symptomatic KOA [82]. In a study by Holz et al., lead-induced osteoarthritis-like phenotype in the articular chondrocytes was demonstrated through disruption of TGF-β signaling, which was confirmed through decreased type II-collagen and increased MMP-13 levels, leading to endochondral ossification and chondrocyte hypertrophy [83]. The data from the farmers in the Yellow River Basin of Henan Province further documented that elevated fluoride levels (over 1.5mg/L water fluoride) could cause fluorosis, which can further lead to osteoarticular degeneration [84]. Polychlorinated biphenyls (PCBs) and dioxins either initiate or worsen OA, possibly by inducing chondrocyte apoptosis via the generation of reactive oxygen species [85].

5.9 Biomechanical factors (Flatfoot, Malalignment, or inappropriate footwear)

Flatfoot has been identified as an independent risk factor for KOA. Studies have shown that flatfoot may be associated with knee joint pain, knee cartilage damage, and could exacerbate disability in KOA patients [86, 87]. This can be explained by weak arch support and limited ability to absorb impacts by flatfoot, which may result in enhanced mechanical stress on the knee, damaging cartilage and soft tissues, and portending risk of KOA. Furthermore, an abnormal joint loading from inappropriate footwear may be associated with KOA severity and progression. Emerging evidence showed a greatly reduced adduction moment in inexpensive, flexible, non-heeled footwear during gait in elderly women [1]. In a double-blinded 3-month intervention study, cushioned footwear alleviated WOMAC pain score after 1 and 3 months and improved functionality compared to a regular shoe in KOA individuals [88]. These results suggest that footwear might be a therapeutic target for KOA. Hence, the shoe type worn by KOA subjects should be examined more closely in terms of their disease contribution.

6. Current therapeutic approaches for KOA

The current non-surgical therapeutic approaches mostly address symptomatic features of KOA, while in severe conditions, only surgical intervention is an effective one [89]. Various guidelines, such as the American College of Rheumatology (ACR), Osteoarthritis Research Society International (OARSI), and American Academy of Orthopedic Surgeons (AAOS), developed by professional societies and academicians, are being used for treatment.

Various treatment outcome measures scales (Supplementary Table 1) are being used to determine the therapeutic impacts.

6.1 Pharmaceutical interventions

The non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular steroids such as methylprednisolone acetate, triamcinolone acetate, triamcinolone hexacetonide, betamethasone acetate, beta-methasone sodium phosphate, and dexamethasone, intra-articular hyaluronic acid, glucosamine, opioids, and duloxetine are some recommended therapeutic agents for KOA treatment [24, 90, 91]. Corticoids (CS) inhibit inflammation, suppress immune response, and significantly lower the level of metalloproteinase, IL-1, prostaglandins, and leukotrienes [24, 92, 93]. The topical and oral NSAIDs are widely recommended; however, the use of acetaminophen is conflicting in different guidelines [94]. Notably, topical NSAIDs are found to be more effective than oral NSAIDs and acetaminophen.

6.2 Antibody-mediated therapy

In addition, antibodies directed against nerve growth factors and inflammatory cytokines like IL-1 are emerging therapies to control pain, inflammation, and OA progression [95, 96]. Intra-articular hyaluronic acid (IA-HA) of different molecular sizes and structures i.e., low molecular weight and high molecular weight IA-HA; notably, high molecular weight IA-HA products are more effective than low molecular weight products [97]. In addition, glucosamine (GS) has shown its therapeutic impact in structural and symptomatic improvement among KOA patients [98]. In addition to the above-mentioned therapeutic agents, the lightweight management, exercise, and lifestyle changes are also recommended to minimize the KOA severity [99]. The above non-surgical approaches are effective in managing symptoms of KOA; however, the associated limited efficacy and side effects limit the potential of pharmaceutical interventions.

6.3 Surgical intervention

The surgical approach is a last resort in case of severe or end-stage KOA. The surgical intervention comes into play when minimally invasive surgery becomes less effective. Total knee replacement surgery or total knee arthroplasty, partial knee replacement surgery or unicompartmental knee arthroplasty, knee osteotomy/high tibial osteotomy or femoral osteotomy, knee arthroscopy, knee cartilage repair, and cartilage restoration are some major surgical interventions for KOA [100]. The choice of surgical procedures depends on factors such as knee function, pain, KOA grade, age, physical activity, and comorbidities [101]. The therapeutic impact and longevity of surgical intervention could be further improved by improving biomechanical and anatomic implant design and alignment. The surgical procedure provides long-term relief. However, surgical complexity, the availability of experts, and expense limit its wide application.

7. Regenerative approach for KOA treatment

Recent developments in regenerative medicine have explored the therapeutic potential of stem cells and their derived exosomes in various disorders. The multipotent, anti-inflammatory, and immunomodulatory properties of mesenchymal stem cells (MSCs) have revealed promising results in KOA treatment [102], due to their differentiation into chondrocytes, cartilage-synthesizing cells [103]. Notably, the autologous chondrocytes isolation, its *in-vitro* expansion, and implantation, i.e., commonly known as autologous chondrocyte implantation (ACI), is a regenerative approach for KOA treatment [104-106]. However, the limited ease of harvest, chondrogenic potential, longer recovery period, and development of periosteal graft hypertrophy restrict ACI as an acceptable regenerative therapy [104, 107, 108]. Notably, MSCs are considered a suitable alternative to autologous chondrocytes due to comparatively easy isolation from bone marrow, umbilical tissue, synovium, dental pulp, neural tissue, adipose tissues, and their chondrocyte differentiation and cartilage regeneration potential [104, 109]. In addition to osteoblast and chondrocytes differentiation potential, the paracrine effect also plays a crucial role in regenerative effects [110]. Induced pluripotent stem cells (iPSCs) are another source, which have been shown to exhibit differentiation potential similar to embryonic stem cells (ESCs)[111]. However, the expenses and time required for reprogramming of somatic cells, lack of genetic stability, and defined clinical-grade quality parameters and potential immunogenicity need to be addressed for clinical recommendation [111, 112]. The ESCs seem an obvious choice for regenerative therapies, but the ethical issues limit their clinical application [113]. In recent years, ADSCs have become a univocal choice over other sources of stem cells due to the presence of multiple harvesting sites, involvement of the liposuction process for autologous ADSCs, high yield, differentiation potential into all germ cell lines, lack of ethical concerns, reduced implant migration, and lower risk of immune response [114, 115].

7.1 ADSCs in KOA Treatment

ADSCs and their derived exosomes, conditioned media (ADSCs-CM), have been explored as the regenerative treatment of various diseases such as cardiovascular disorders, osteoarthritis graft versus host disease (GvHD), systemic lupus erythematosus, multiple sclerosis, and other autoimmune disorders [116]. Additionally, ADSCs have also shown their efficacy in spinal cord injury, tendon reconstruction, skeletal repair, and bone and cartilage regeneration [116-120]. ADSCs are isolated by liposuction/ lipoaspiration or surgery and then digested through mechanical, enzymatic, or chemical means to prepare stromal vascular fraction (SVF) [121, 122]. A clinical study implicates that the intra-articularly injected SVF lowers the expression of pro-inflammatory molecules and catabolites, i.e., IL-1β, IL-6, IL-8, and MMP-2, along with elevated levels of IL-10 and IGF-1 [123].

Adipose-derived SVF therapeutic efficacy is affected by the lesion size and number of SVF cells [124]. Further, ADSCs are found in low concentration in the SVF, and to increase their presence, the SVF is further expanded and purified for ADSCs isolation [125]. ADSCs are characterized by the high expression of molecular markers, i.e., CD44, CD73, CD90, CD105, and CD106, along with lower expression of CD31, CD45, CD133, CD144, and CD146 of endothelial and hematopoietic markers [125, 126]. The NANOG, OCT4, and SOX2 biomarkers confirm their pluripotency [126, 127]. A recent study revealed an efficient method for ADSC isolation by a direct membrane (hydroxyapatite-treated nonwoven fabric) migration method without employing enzymatic digestion via collagenase, under serum-free medium, and collected sufficient cell numbers for clinical application. [128]. The isolated cells were found to be positive for CD44, CD73, CD90, and CD105 and negative for CD11b, CD34, CD45, CD80, and HLA-DR with trilineage differentiation potential (adipocytes, osteocytes, and chondrocytes). After a year of treatment, the ADSCs could significantly lower the Western Ontario and McMaster Universities Arthritis Index (WOMAC, from 32.9 to 9.4 of treatment), Visual Analog Scale (VAS, from 5.9 to 2.1) among KOA patients [6]. However, a randomized, single-blind, multiple-centre clinical trial showed that allogeneic adipose-derived stem cells (ADSCs) treatment is safe and effective in reducing WOMAC pain score after 24 weeks of treatment without any significant incidences of serious adverse events [129]. The schematic of ADSCs-mediated KOA therapy is represented in Figure 2.

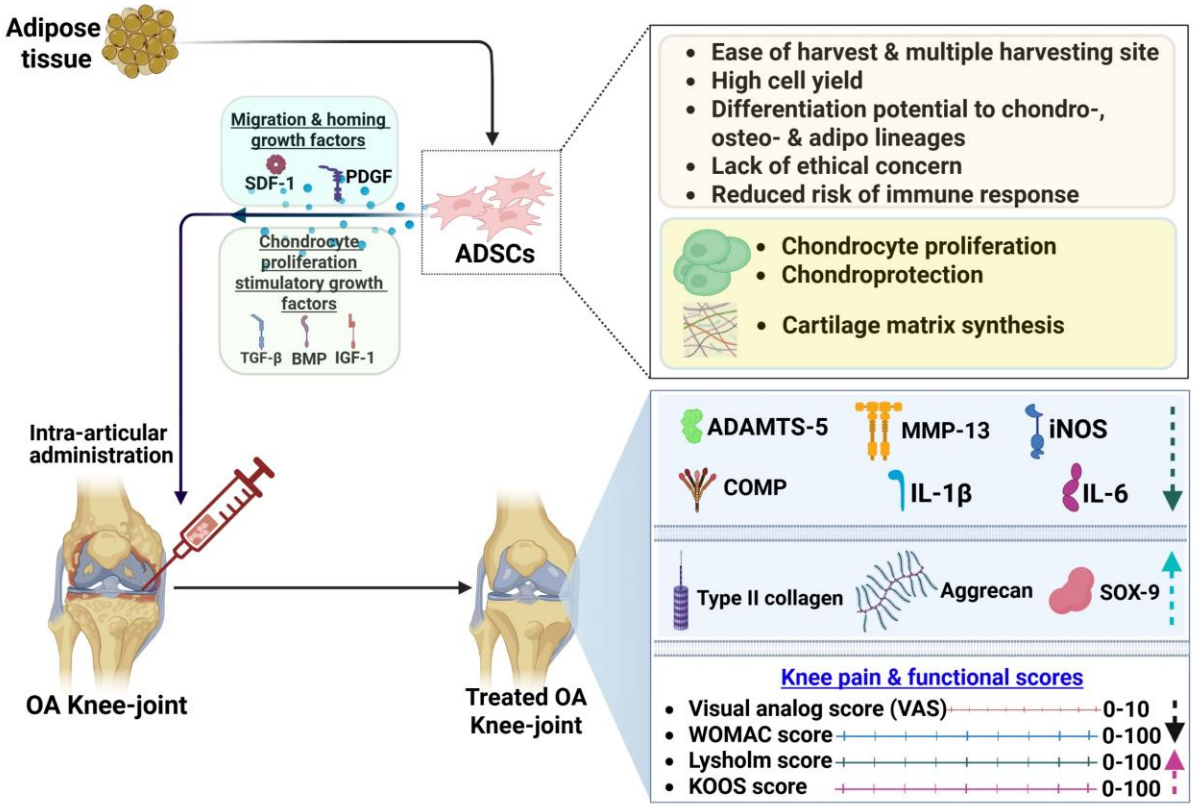

Figure 2. Diagrammatic representation of ADSCs-mediated treatment of KOA. Adipose tissue isolated stem cells exhibit reparative regeneration activities by migrating and homing to the injured site and inhibiting inflammatory signalling, and enhancing levels of type II collagen, aggrecan (proteoglycan), and SOX-9. The clinical outcomes are determined by various knee pain and functional scores. The downward green and upward arrow indicate inhibited and stimulated levels, respectively. Further, the improvement in knee pain and function is indicated by reduced VAS and WOMAC scores (downward black arrow) and increased Lysholm and KOOS scores (upward pink colored arrow). KOA: Knee osteoarthritis, SDF: Stromal-derived factor, PDGF: Platelet-derived growth factor, TGF-β: Transforming growth factor-β, BMP: Bone morphogenetic proteins, IGF-1: Insulin-like growth factor 1, ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs, MMP: Matrix metalloproteinase, IL-1β: Internleukin-1β, iNOS: Inducible nitric oxide synthase, COMP: Cartilage Oligomeric Matrix Protein, VAS: Visual analog score, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, KOOS: Knee Injury and Osteoarthritis Outcome Score (KOOS). Created in BioRender. Dubey, N. (2025) https://BioRender.com/x0yrn2o.

Clinically, even SVF in the presence of activated platelet-rich plasma (PRP) reduced pain score (7.6±0.5 to 3.5±0.7) [130], increased Lysholm score (61±11 to 82±8.1), with thicker cartilage after 6 months of treatment without any severe adverse events. Notably, a double-blind randomized self-controlled trial in a 12-month follow-up demonstrated a safer profile of SVF and found therapeutic impact similar to HA in repairing cartilage, which was evidenced by improved VAS, WOMAC scores, and range of motion in 16 patients with bilateral symptomatic KOA (K-L grade II to III)[131]. Similarly, the autologous ADSCs treatment and arthroscopic debridement in early KOA patients (KL grade: II-III) improved International Knee Society (IKS) knee score (57.2 to 83.0), reduction in VAS (8.5 to 5.1) [132]. Further, a phase II triple-blinded, placebo-controlled, randomized trial demonstrated that a dose of 1×10^8 allogeneic ADSCs reduced cartilage oligomeric matrix protein and hyaluronic acid levels, along with a significant reduction in inflammatory markers [133]. Tibial and femoral articular cartilage thickness was also noted. In sodium iodoacetate-induced KOA in the left knee joint of rats, 50μL SVF (5×10^6 cells) and ADSCs (1×10^6 cells) remarkably recovered the articular cartilage surface, which appeared nearly normal, smooth, and bright at 14 days with IL-1β level, indicating the anti-inflammatory and regenerative potential [134]. In a rabbit anterior cruciate ligament transection (ACLT) model, intra-articularly administered ADSCs inhibited degenerative cartilage progression at 8 weeks by homing to synovium and down-regulated MMP-13 expression [135]. The finding reports the chondroprotective, chondrocyte proliferation, and cartilage matrix protection role of ADSCs.

Notably, the intra-articular injection of human ADSCs resulted in reduced levels of ADAMTS-5, MMP-13-, iNOS, IL-1β-, and IL-6- positive cells, while an increase in CD206- and type II collagen positive cells, implying anti-osteoarthritic potential of ADSCs. ADRCs promote macrophage polarization toward M2 in chondrocytes, indicating the role of M2 in modulating OA treatment. MSCs suppress immune response by releasing transforming growth factor-β (TGF-β), IL-6, and prostaglandin (PGE) E2. These factors retard T-cell proliferation/function, induce senescent-like NK cells, which reprogram proinflammatory M1 state macrophages to the conducive M2 phenotype [136, 137]. While exerting reparative regeneration impacts, the MSC-derived secretome, containing bioactive factors like stromal cell-derived factor-1 (SDF-1) and platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), bone morphogenetic proteins (BMPs) and insulin-like growth factor-1 (IGF-1), which play a key role in their paracrine effects etc.

SDF-1, also called CXCL12, plays a key role in recruiting ADSCs to the KOA joint by binding CXCR4 receptors, elevating cell homing and migration to damaged cartilage, where it promotes tissue repair and reduces inflammation [138]. PDGF stimulates ADSC proliferation and differentiation into chondrocytes, facilitating extracellular matrix synthesis and cartilage regeneration in knee OA models [139]. Another growth factor, transforming growth factor-β (TGF-β), induces chondrogenic differentiation of ADSCs, upregulating collagen II and aggrecan expression to repair osteoarthritic cartilage defects [140]. Further, bone morphogenetic proteins (BMPs) enhance ADSCs osteochondral differentiation, promoting bone and cartilage synthesis in KOA, often synergistically with TGF-β [141]. Insulin-like growth factor-1 (IGF-1) is upregulated by ADSCs in KOA models, ameliorating symptoms by rescuing chondrocytes from apoptosis and stimulating matrix production.

In another clinical open-label phase I trial, a single intra-articular injection of 5×10^7 cells autologous infrapatellar fat pad-derived mesenchymal stem cells (IFP-MSCs) significantly reduced pain and MRI Osteoarthritis Knee Score average (100.2 to 85.0), leading to improved knee function at 48 weeks follow-up [142]. Thus, the above evidence, particularly clinical studies (Table 1) confirm SVF and ADSCs' therapeutic value in KOA treatment.

7.2 Synergistic therapeutic approaches of ADSCs and biomaterials

Synthetic and natural biomaterials are being used to deliver regenerative cells for restoring cartilage structures [143]. The recommended properties of biomaterials include high biocompatibility, porous structure, rapid biodegradation, and excellent mechanical strength. Hydrogels, sponges/foams, fibrous matrices, and fibrous meshes/scaffolds are some available choices used for the delivery of ADSCs for KOA treatment. Alginate, the acellular matrix, collagen, gelatin, and HA are the natural biomaterials, while polyethylene glycol, poly-caprolactone, poly N-isopropyl acrylamide (PNIPAM), and poly(L-lactide-co-glycolide) (PLGA) are the synthetic biomaterials used for the delivery of regenerative cells for KOA treatment [144]. In a study, the plasmid DNA containing SOX-5, -6, and -9 genes in a PLGA scaffold impregnated with ADSCs was administered in the rabbit. The results showed an increased expression of SOX and COL2A1 genes, while a decrease in COL10A1 gene, indicating the efficacy of this combinatorial treatment in OA [145].

Table 1. Summary of clinical trials of ADSC-based treatment of KOA.

Study design	Sample size	Intervention (dose, frequency)	Comparator	Primary outcome	Main findings	Follow-up duration	Safety profile
Prospective pilot safety and feasibility study [6]	6	Adipose-derived SVF cells (3c.c.)	NA	Improved WOMAC ($P < 0.02$), VAS ($P < 0.001$) ROM and TUG	All patients achieved full activity with reduced knee pain.	3-month, 1-year	No adverse events
Phase I/II, randomized, active-control, single-blind, multiple-center clinical trial [129]	57 64 M, (n=15) 32 M (n=17) [16 M, (n=17)]	Allogeneic ADSCs (ELIXCYTE® 64×10^6 cells, 64 M; ELIXCYTE® 32×10^6 cells, 32 M; ELIXCYTE® 16×10^6 cells	HA	Improved WOMAC pain score, VAS, KSCRS	ELIXCYTE® was efficacious, safe, and well-tolerated	24-week, 96-week	No AEs or SAEs or SUSAR
Retrospective non-randmized-controlled study [132]	52	Microfragmented adipose tissue product (10–15 mL)	NA	IKS knee score, IKS function score VAS	96.2% of patients were satisfied (good or excellent improvements in function and/or pain)	3,6, and 12 months	AEs were only associated with the harvesting procedure. 3 patients developed a transitory haematoma of the abdominal area
Phase II, triple-blinded, placebo-controlled, randomized trial [133]	40 [allogeneic ADSCs, (n=20); placebo normal saline, (n=20)]	100×10^6 allogeneic ADSCs,	Placebo (normal saline)	Improved WOMAC, VAS, KOOS,	Reduced HA and COMP levels in blood serum	3, 6, and 12 months	AE: 2 patients suffered swelling of the injection site in the joint. No SAE
Phase 1, open-label, non-comparative and single-center clinical trial [142]	12	IFP-MSCs (5×10^7 cells)	NA	Improved VAS, IKDC questionnaire, and KOOS	Clinically significant pain and functional improvement	1, 4, 12, 24, and 48 weeks	41 AEs (Major include joint swelling, arthralgia, joint noise, wound complications, etc.)
Prospective, observational study [165]	44 [HTO with PRP, (n=23), PRP+ADSCs, (n=21)]	PRP (1303.27 375.2 $\times 10^3$ /mL) ADSC (4.11×10^6 cells)	PRP	Improved KOOS, VAS, Lysholm scores	Compared to PRP, synergistic ADSC+PRP showed significantly improved clinical results	3 months and 1 year	NA

SVF: Stromal vascular fraction. HA: Hyaluronic acid, ROM: Range of motion. TUG: timed up-and-go. WOMAC: Western Ontario and McMaster Universities Arthritis Index, VAS: Visual analog score, AE: Adverse events. SAE: Serious adverse event, SUSAR: Suspected unexpected serious adverse reaction, KSCRS: Knee Society Clinical Rating System. KOOS: Knee osteoarthritis outcome score, SF-36: Short Form 36, COMP: cartilage oligomeric matrix protein, IFP-MSCs: Infrapatellar fat pad-derived MSCs, IKDC: International Knee Documentation Committee (IKDC), PRP: Platelet-rich plasma, HTO: high tibial osteotomy, NA: Not available.

Further, the amniotic membrane (AM) has also been employed to deliver ADSCs in the knee joint of the OA rat model, in which AM localized the ADSCs at the injected site and resulted in cartilage regeneration, leading to chondroprotection and a significant reduction in inflammation [146]. An extracellular matrix (ECM) having hydrogel properties is used to deliver ADSCs overexpressing transforming growth factor-β1 (TGF-β1) [147]. The ECM-hydrogel improved cell survival, reduced tumor necrosis factor-alpha (TNF-α) expression, upregulated levels of aggrecan and collagen II, and increased paracrine effect in the rat OA model [147]. The cumulative effect of these molecular changes resulted in suppressed cartilage degeneration, subchondral bone loss, and inflammation in the knee joint. Notably, a dog-model-based study suggests that a nanofiber scaffold of PLGA lowers the therapeutic efficacy of stromal vascular fraction (SVF) [148]. However, the combined HA and adipose-derived SVF improved the therapeutic impact of HA and the rapid regeneration of cartilage in osteochondral defects in the rabbit model [149]. Intra-articularly injected ADSCs and chondrocytes with platelet-rich fibrin releasates augmented acute osteochondral defects in the white rabbit KOA model, indicating [150]. A recent progress in cell sheet engineering was prepared in a scaffold of biomaterials such as collagen type-I, L-ascorbate 2-phosphate (A2-P), and transplanted in normal ECM and cell-cell junctions, and enhanced cell viability, increased influx of cells, improved stemness, and transdifferentiation potential [151-155]. The ADSCs sheet in the rabbit model has also been demonstrated to exhibit meniscal regeneration with improved elastic modules, increased contact area, increased volume, improved histologic score, and low peak pressure [156, 157]. Notably, the combined PRP and ADSCs sheet prepared by using ascorbic acid maintains the chondrogenic potential of ADSCs by retaining the expression level of aggrecan, collagen type-II, and SOX9, thereby effectively promoting chondrocyte differentiation and suppressing the KOA in rabbits [158]. Thus, it is expected that biomaterials improve the therapeutic efficacy of SVF and ADSCs.

7.3 Other ADSCs-based combinatorial therapies

Extracorporeal shockwave therapy (ESWT) has been demonstrated to exert a therapeutic effect on pain, subchondral bone, cartilage, and joint activities in KOA progression [159]. The combination of ESWT with ADSCs and human umbilical cord Wharton's jelly-derived mesenchymal stem cells has been evaluated for their KOA treatment. Of these combinations, the synergistic ESWT and ADSCs treatment was found to be superior in improving bone volume and trabecular thickness [160] with upregulated expression of bone morphogenic protein (BMP)-4, and downregulated expression of platelet-derived growth factor (PDGF)-BB. The combined ESWT and ADSCs also showed higher efficiency in regulating the expression of TGF-β, sex determining region Y-box (SOX)-9, and runt-related transcription factor (RUNX)-2. Similarly, the synergistic therapeutic effect of ADSCs (2×10^6 cells) and SWT (0.25 mJ/mm^2 with 800 impulses) resulted in a considerable elevation in bone volume, trabecular number, and thickness, along with a significant decrease in OARSI and synovitis score [161]. The combined ADSCs and SWT could decrease tumor proteoglycan (PRG)-4 and tumor necrosis factor-inducible gene (TSG)-6, downregulate inflammation-induced bone morphogenetic protein (BMP)-2 and BMP-6, along with elevated levels of type II collagen, and tissue inhibitor matrix metalloproteinase (TIMP)-1[161]. Intraarticular injection of suspension allogenic ADSCs (1×10^6 Cells) and 1% xanthan gum (XG) in the rat model improved weight-bearing percentage and lowered the level of TNF-α, IL-1β, MMP-3, and MMP-13 in synovial fluid, which were superior to ADSCs alone [162]. The XG promoted ADSCs proliferation and significantly reduced pain, cartilage degeneration, and inflammation. Notably, ADSCs treatment with the synovial fluid improved cell viability, and overexpression of FOSL1 genes is associated with increased cell viability [163]. In rats, synergistic treatment with hyperbaric oxygenation (HBO) and allogenic ADSCs (1×10^6) resulted in cartilage regeneration and a decrease in knee joint damage score; and this treatment was found to be superior to any of the standalone treatments of HBO or ADSCs [164].

Further, platelet-rich plasma (PRP) is considered a promising candidate in regenerative therapy due to its contained bioactive growth factors. In a clinical study, the combined administration of ADSCs and PRP in open-wedge high tibial osteotomy showed significant recovery in cartilage structure, knee osteoarthritis outcome score (KOOS), and reduction in VAS pain score, and hence the improvement in knee injury [165]. The PRP induces ADSCs proliferation, chondrogenic differentiation with overexpression of aggrecan, collagen II, and Sox9, resulting in improved cartilage regeneration [166]. The exposure to BMP-6 and TGF-β3 to ADSCs may also enhance the expression of aggrecan, cartilage oligomeric protein, collagen I, collagen II, Sox9, chondroadherin, and fibromodulin, resulting in significant improvement in cartilage score and joint function in the sheep KOA model [167]. A 12-month clinical study among grade II and III KOA patients further confirmed the synergistic effect of PRP and ADSCs injection in improving cartilage thickness and motor function of the knee joint [168]. A recent clinical study demonstrated that multiple intra-

articular dose of ADSCs induces severe arthritis, and the presence of an antibody against histone H2B is detected post-treatment [169]. However, this is contradicted by the finding that the periodic injection of ADSCs sheet inhibited the progression of OA in white rabbits by homing to the synovium and protecting chondrocytes [151]. Further, a nanoparticle was used to overexpress the SOX-6, -9, and silence the angiopoietin-like 4 (ANGPT4) genes in ADSCs, resulting in increased expression of COL2 gene, decreased expression of MMP3, cyclooxygenase (COX-2), and MMP13 genes along with improved chondrogenesis and inhibited inflammation in the KOA rat model [170]. Taken together, these synergistic approaches (Figure 3) revealed their potential therapeutic effect in ameliorating osteoarthritic pathological factors in the knee joint (Table 2).

Table 2. Summary of synergistic ADSC and other therapeutic approaches to enhance the therapeutic impacts in KOA.

ADSC type/ form	Treatment (duration)	Model name	Therapeutic outcomes
ADSC sheet [158]	PRP (12 weeks)	Rabbit	• Reduced OARSI scores, proteoglycans, • Decreased MMP-1, MMP-13, & ADAMTS-4 • Attenuated KOA progression
Autologous ADSC [161]	Shockwave (5 weeks)	Sprague–Dawley rats	• Elevated bone volume, trabecular number, and thickness, along with significantly decreased OARSI and synovitis score • Decreased PRG-4 and tumor necrosis factor-inducible gene (TSG)-6, • Downregulated inflammation-induced bone morphogenetic protein (BMP)-2 and BMP-6, • Elevated levels of type II collagen & TIMP-1
Allogeneic ADSC [162]	Xanthan gum (4 weeks)	Wistar rat	• Increased ADSC proliferation • Reduced OA pain, smooth appearance of articular cartilage with maintained integrity • Suppressd IL-1β, TNF-α (inflammation), MMP-3 and MMP-13 (matrix-degrading enzymes)
ADSC [164]	HBO (3 weeks)	Wistar albino rat	• Greater cartilage thickness with a smooth surface and higher proteoglycans • Significantly reduced H_2O_2 level (prooxidative marker) • Suppressed TNF- α and IL-6 • Enhanced GSH and CAT activities

ADSC: Adipose-derived stem cells, KOA: Knee osteoarthritis, PRG-4: Tumor proteoglycan, TSG-6: tumor necrosis factor-inducible gene, BMP: Bone morphogenetic protein, TIMP-1: Tissue inhibitor matrix metalloproteinase-1. GSH: Glutathione, CAT: Catalase.

7.4 ADSCs-Exosomes and KOA treatment

Exosomes (Exos) represent a cell-free, off-the-shelf regenerative therapy, which could eliminate the risks of immune rejection, tumorigenicity, and pulmonary embolism associated with whole-cell implantation, potentially transforming KOA management from palliative to disease-modifying (Figure 4). However, to date, no exosome-based therapy has received regulatory approval for KOA, in contrast to certain adipose-derived cell products with limited approval or conditional marketing authorization in certain countries. ADSCs-Exos are extracellular vehicles (EVs) that have a cup shape and a diameter ranging from 30-150nm, with a density of 1.1-1.18 g/mL. It contains biomolecules such as proteins, cytokines, metabolites, nucleic acids, lipids, cytosolic and cell surface proteins [171-173]. Exosomes are distinguished by the presence of various biomarkers, such as ALIX, TSG101, CD9, CD63, CD81, CD109, CD166, etc. [173-175]. In vitro studies have demonstrated the efficacy and safety of Exo in the treatment of orthopaedic, neurodegenerative, cancer, cardiovascular, and other diseases [173]. The therapeutic potential of ADSCs-exosomes (ADSCs-exo) for KOA has also been demonstrated in various studies. Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells are promising in preventing KOA by elevating cartilage regeneration in a rat model. This was executed by exosomes carrying Wnt5a and Wnt5b, which activated YAP through the alternative Wnt signalling pathway, leading to increased chondrocyte proliferation and migration with the side-effect of decreasing ECM secretion [176].

Recently, it has been demonstrated that ADSCs-derived small extracellular vesicles (sEVs) could also modulate gene expression and release of chondrocyte and synoviocyte proteins [177], inhibiting the inflammatory NF-κB pathway and expression of MCP-1. Of note, the exosomal miR-429 derived from ADSCs attenuates chondral injury in KOA through autophagy by targeting

FEZ2. This is possible by absorption of ADSCs-exos miR-429 in the chondrocytes, leading to their proliferation [178].

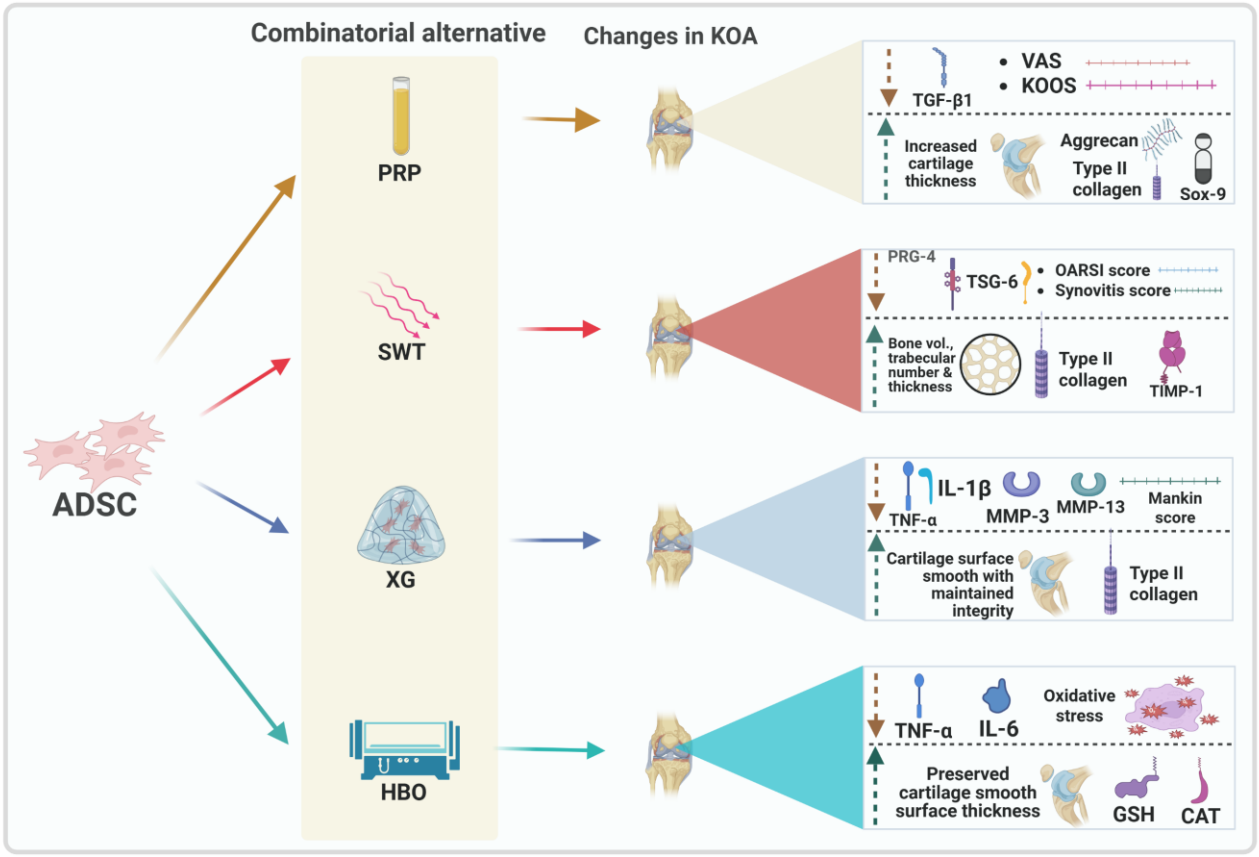

Figure 3. Synergistic ADSCs and other therapeutic approaches to enhance the therapeutic impacts in KOA. The improvements are assessed based on the reduction in inflammatory cytokines and the preservation of cartilage integrity. KOA: Knee osteoarthritis, PRP: Platelet-rich plasma, SWT: Shockwave therapy, XG: Xanthum gum, MMP: matrix metalloproteinase, TIMP: Tissue inhibitor of metalloproteinase, TNF-α: Tumor necrosis factor-α, IF-6: Interleukin-6, HBO: Hyperbaric oxygenation, PRG-4 and TSG-6. PRG-4: tumor proteoglycan-4, TSG-6: tumor necrosis factor-inducible gene, GSH: Glutathione peroxidase, CAT: catalase. The various scales used, like OARSI, KOOS, and Mankin score, synovitis scores. OARSI: Osteoarthritis Research Society International, KOOS: Knee Injury and Osteoarthritis Outcome Score. Created in BioRender. Dubey, N. (2025) https://BioRender.com/uk0gorg.

The hypoxia could further ameliorate the therapeutic efficacy of ADSCs-exos. Hypoxia-treated ADSCs-exo attenuates lumbar facet joint OA by abrogating aberrant H-type vessel synthesis in the subchondral bone of C57BL/6 male mice [179]. This indicates that hypoxic preconditioning could further enhance the therapeutic effects of ADSC-exo even in KOA. Another study showed that exosomes secreted from ADSCs overexpressing miRNA-338-3p protected the OA joint by reducing inflammatory stress via suppressing the expression of IL-6, IL-1β, prostaglandin E2 (PGE2), and TNF-α, along with promoting chondrocyte proliferation *in vitro* [180]. ADSCs-exosome expressing miR-93-5p also inhibits inflammation, apoptosis, and autophagy in IL-1β-treated chondrocytes via activating PI3K/AKT/mTOR signaling pathway and alleviating KOA [181]. ADSCs-exo promotes proliferation and chondrogenesis, evidenced through increased collagen type II and β-catenin in periosteal cells and retard inflammation by upregulating miR-145 and miR-22 and inhibiting Wnt/β-catenin signalling [182].

Studies reveal that ADSCs-exos derived from the infrapatellar fat pad (Exos-IPFP) may also be a potential candidate for ameliorating OA. The injectable hydrogel microparticles represent a sustained local drug release system for long-term therapy by continuous Exos release. In a seminal study, ADSCs^{IPFP}-exo abundant miR-100-5p could protect articular cartilage and maintain its homeostasis in addition to ameliorating gait abnormalities by regulating inhibition of the mTOR-autophagy pathway in OA mice [183].

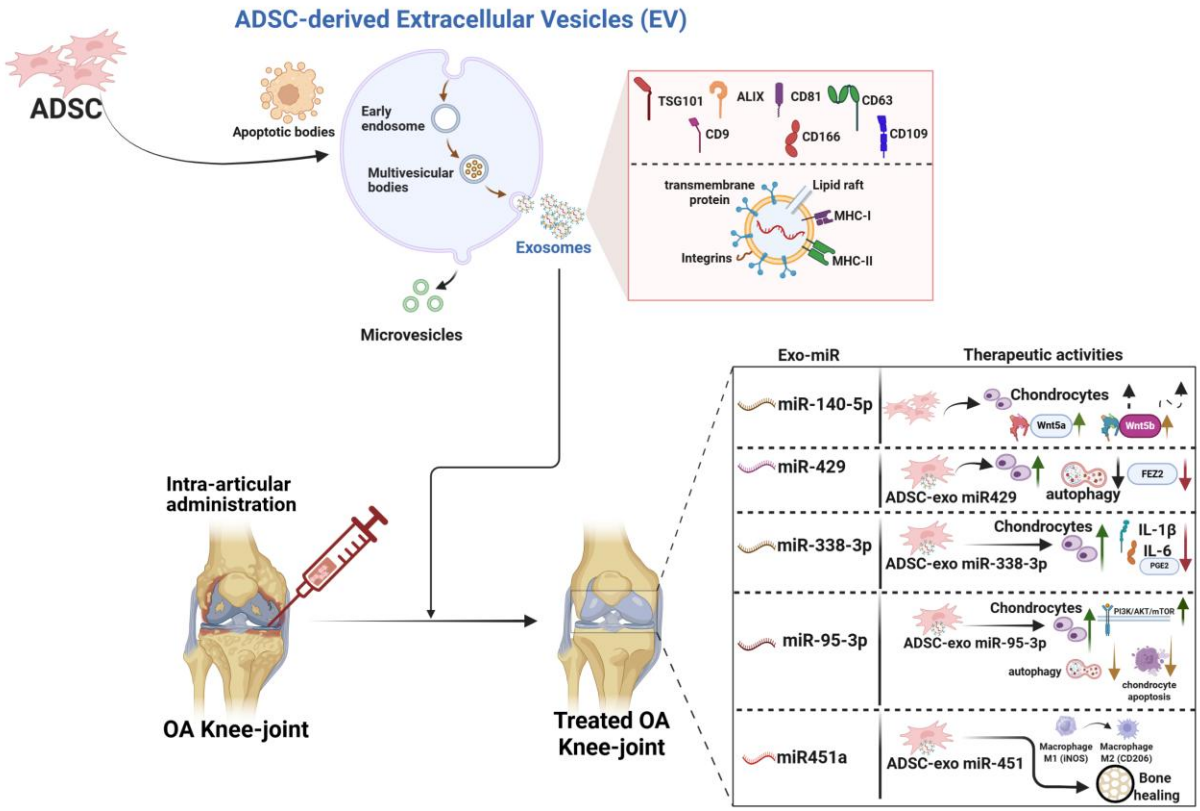

Figure 4. ADSCs exosomes (ADSCs-exo)-mediated acellular therapy in KOA. Exo isolated from ADSCs are characterized by the presence of biomarkers such as TSG101, ALIX, CD81, CD9, CD166, and CD109, etc. The major exosomal microRNAs like miR-140-5p, miR-429, miR-338-3p, miR-95-3p, and miR-451a, etc., have been reported to exert therapeutic impacts in KOA through various pathways like Wnt signalling, FEZ2 pathway, PI3K/AKT/mTOR signalling. Created in BioRender. Dubey, N. (2025) https://BioRender.com/rrle5rq.

ADSCs-exo could be induced by kartogenin (a small bioactive molecule), leading to increased expression of chondrogenic genes in ADSCs (Aggrecan, Collagen III, Collagen II, and SOX9), and significantly reduced expression of chondrolysis-associated genes (MMP-3, ADAMTS4, and ADAMTS5) [184]. Interestingly, studies have also investigated the therapeutic potential of tissue origin (rat's adipose, bone marrow, and synovium)-based EV, and shown that the ADSCs-EVs induced more proliferation, migration, and differentiation of BMSCs towards chondrogenic and osteogenic lineages in a mouse model when compared to BMSC-EVs or SMSC-EVs [185]. The proteomic analysis of this study revealed underlying mechanism including actin cytoskeleton, focal adhesion, cAMP, ECM-receptor interaction, and PI3K-Akt signalling pathways Apart from the infrapatellar fat pad, the subcutaneous fat-derived stem cell exosomes ($MSCs^{SC}$-Exos) have also shown their cartilage regeneration potential via miR-199a-3p mediated inhibition of the mTOR signalling pathway in destabilization of the medial meniscus (DMM) and anterior cruciate ligament transection (ACLT) surgery-induced OA rat model [186]. Further, chondrocyte-binding peptide (CAP) binding $MSCs^{SC}$-Exo effectively delivers miR-1991-3p in chondrocytes both *in vitro* and *in vivo*.

Genomic changes after human ADSCs-derived exosome administration in monosodium iodoacetate-induced OA rats have also been identified and a microarray analysis revealed that ADSCs-exo induce upregulation of genes associated with angiogenesis, cell cycle, inflammatory response, cell death, immune response, cell differentiation, DNA repair, cell proliferation, RNA splicing, and secretion functions, indicating the role of these molecular pathways in exosomes-mediated OA treatment [187]. Bony defects in the knee, like subchondral lesions, usually accompanied by inflammation, may be repaired by implanting biomaterials to stimulate bone metabolism and new bone synthesis. In this line, a study showed that ADSCs-exo could also promote bone healing via miR-451a/migration inhibitory factor (MIF) by regulating M1/M2 macrophage

phenotypic polarization, indicating the role of ADSC-exo in immune regulation and immune metabolism in reparative regeneration [188]. In recent years, bone defect repairing approaches using exosome-modified tissue engineering scaffolds have been explored. In a seminal study, ADSCs-exos modified with gelatin sponge/ polyamide scaffold (GS-PDA-Exos) improved the proliferation, migration, and osteogenic differentiation of BMSCs. The osteogenic runt-related transcription factor 2 (Runx2), osteocalcin (OCN), Osterix (OSX), osteopontin (OPN), and Collagen type I (COL1) during osteogenesis induction in BMSCs, implying the ADSC's potential in repairing subchondral bone defect in KOA [189]. In summary, ADSCs-exos are emerging as an effective cell-free regenerative therapeutic agent, which can mediate their effects (Table 3) mostly via miRNAs modulating inflammation, chondrocyte protection, modulating ECM synthesis, regulating autophagy, and apoptosis. However, these therapeutic potentials of ADSCs-exos need to be further preclinically and clinically validated, and effective protocols for the treatment should be well-established.

Table 3. List of exosomal miRNA-based studies for the treatment of KOA.

Exosomal miRNA	Target molecule/pathway	Mechanism of action	Therapeutic outcome
miR-140-5p [176]	Wnt5a and Wnt5b, which activated Yes-associated protein (YAP)	Wnt signalling pathway	Enhanced proliferation and migration of articular chondrocytes, and prevented KOA
miR-429 [178]	Promote autophagy of chondrocytes by targeting FEZ2	This effect is possible by absorption of ADSCs-exos miR-429 in the chondrocytes	Promoted chondrocyte proliferation
miRNA-338-3p [180]	Suppress the expression of IL-6, IL-1β, prostaglandin E2 (PGE2), and TNF-α. Inhibit RUNX2 expression	Inhibit MMP3 and MMP13 expression and increase Col2a1 and aggrecan	Inhibit the degradation of chondrocytes
miR-93-5p [181]	Inhibit autophagy and apoptosis of IL-1β-treated chondrocytes, and upregulate ADAMTS9	Activate the PI3K/AKT/mTOR pathway	Suppressed inflammation and alleviated OA

7.5 Comparative efficacy of ADSCs in KOA treatment

Some of the previous studies have compared the therapeutic potential of ADSCs with other cell types. The therapeutic outcomes were found to be more effective in KL grade 2 patients in comparison to grade 3 and 4 patients. In the lateral meniscectomy-induced sheep OA model, the three different cellular therapies, including ADSCs, SVF, and amniotic epithelial stem cells (AECs), were administered for 3 months. All the regimens improved cartilage surface and suppressed proinflammatory cytokines in synovial fluid; however, the ADSCs were found to be inferior to SVF [190]. However, studies also exist showing no significant clinical differences in therapeutic outcomes between ADSCs and BMSCs mediated therapy, and showed similar improvement in KOOS, Oxford Knee Score (OKS), and VAS [191].

Various pre-clinical and clinical studies have demonstrated the therapeutic efficacy of MSCs in KOA treatment. However, low cell viability and retention limit the therapeutic efficacy of stem cells. To overcome the above limitation and increase the cartilage regeneration potential, pre-treatment of stem cells with specific molecules, hypoxic conditions, and cytokines could improve cell survival, adhesion, migration, and homing [192]. In addition, genetic modification, expression of antibodies on the surface of MSCs, magnetic stem cell targeting, and peptide functionalization of MSCs for targeted treatment. ADSCs stimulated by type V collagen (Col V) induce a significant increase in type II collagen and aggrecan in the degenerative area of surgically induced osteoarthritic rabbit articular cartilage (OA), while Pau5fl is downregulated in the rabbit OA model [193].

Besides exo, the long non-coding RNAs (LncRNAs), containing more than 200 nucleotides in length, play a crucial role in regulating transcription factor binding, chromatin modification, competent endogenous and other post-transcriptional mechanisms resulting in improved osteoblast differentiation [194]. For instance, the upregulation of LncRNA H19 in ADSCs promotes chondrocyte differentiation, and the regulatory function of H19 is associated with the regulation of the STAT2 pathway [195]. Similarly, another study demonstrated the promoting role of lncRNA NONHSAT030515 in the chondrogenic differentiation of hADSCs into chondrocytes by regulating miR-490-5p/bone Morphogenetic Protein Receptor, Type II (BMPR2)[196].

8. Future prospects and challenges

Besides modifiable factors such as obesity (30Kg/m^2), joint injury (meniscal tears and ACL rupture, etc.),

occupations (farming, squatting, kneeling), the role of emerging etiologies like diabetes mellitus, hypertension/blood pressure, gut lipidemia, gut microbiome dysbiosis, vitamin D deficiency, smoking, BMD, ultra-processed food, and flatfoot, and environmental pollutants (Fluoride, lead, polychlorinated biphenyl etc.) need to be explored with detailed mechanistic insight. The ADSCs-mediated regeneration of cartilage and KOA treatment is considered a potential therapeutic alternative. The comparatively easy harvest of adipose tissues for isolation of autologous ADSCs and no ethical conflict have rendered ADSCs a preferred choice for regenerative treatment of KOA.

Importantly, the optimal patient selection for ADSCs therapy in KOA is critical to augment efficacy and reduce risks, affected by disease severity, age, body mass index (BMI), and comorbidities. For disease severity, ADSCs injection seems to respond better in the early-stage OA (KL grades 1–2), by significantly improving cartilage volume and pain score. This could be attributed to residual tissue viability [197]. Whereas grades 3–4 may show limited efficacy, owing to advanced cartilage loss and subchondral bone changes. Patients aged 18-70 appear to respond better; however, those under 65 might see longer-term benefits from cell proliferation [198]. Exclusion over 75 reduces the risks from frailty and suppressed healing capacity. Further, a systematic review of 23 studies documented that BMI <30 kg/m² is optimal, as obesity (BMI >30-35) promotes inflammation and stem cells obtained from obese patients exhibit elevated expression of interleukin-1, interleukin-6, and tumor necrosis factor-α, greater macrophage content [199], with decreased proliferative ability, impaired differentiation, and migration properties [200]. Hence, the trials routinely exclude BMI >30 to improve outcomes and safety. Comorbidities like diabetes mellitus further complicate therapeutic response, with uncontrolled hyperglycemia inhibiting ADSCs viability and anti-inflammatory effects, necessitating pre-treatment optimization. On the contrary, patients without metabolic syndrome show better pain relief. Taken together, personalized selection focusing on early OA, younger age, normal BMI, and minimal comorbidities may elevate ADSC therapy success rates, guiding future randomized trials to refine inclusion criteria.

The current genetic modification techniques and preconditioning have made it possible to further improve the therapeutic outcomes. Further, the appropriate choice of biomaterials for the scaffold and delivery of ADSCs at target sites improves the cell viability and homing. Recent attempts have also been made to understand the role of ADSCs-derived EVs, such as miRNAs and lncRNAs, in chondrogenic differentiation. ADSCs-exos, being a carrier of several important biomolecules, and their role in regulating various molecular pathways, have opened another regenerative method to treat KOA. The ADSCs are a significant candidate for providing not only symptomatic relief but also for remodeling KOA. However, the lack of clinical studies, uniform therapeutic procedures, and their compatibility with current treatments, specifically surgical approaches, needs to be extensively studied to establish the ADSCs treatment procedures. While stem cell banks are well-established, clinical-grade banking infrastructure for adult somatic stem cells, such as ADSCs, aimed at regenerative medicine applications, remains in a relatively nascent stage, with limited standardization and global accessibility. Hence, they need to be tested over time in providing safe and affordable biomaterials for regenerative therapies. In addition, the development of allogenic ADSCs for regenerative therapy will further minimize the invasive procedure in regenerative treatment. Thus, more scientific and clinical works are required to establish the ADSCs-mediated KOA treatment. Additionally, increasing the understanding of molecular changes in regenerative treatment will also contribute to developing standard clinical procedures. Most preclinical and clinical studies report the safety of ADSCs therapy; however, these findings are limited to a single dose of ADSCs, and some studies have mentioned the complications and adverse events with multiple intra-articular injections of ADSCs. Thus, addressing this issue is required to recommend the repetitive use of ADSCs.

Importantly, ADSCs and derived exosome therapies for KOA require standardization, and regulatory strategies to enable clinical translation, leveraging exosomes' benefits in reduced immunogenicity and off-the-shelf potential. Large phase III randomized clinical trials with over 5-year follow-up are needed to validate long-term cartilage regeneration and pain relief. Exosome-specific studies should prioritize miRNA cargo mechanisms, surface modifications for targeting, and biomarkers for response prediction. Dose-response and combination therapies address variability. Hence, the optimal ADSCs doses should be standardized with GMP enzymatic/mechanical processing, ensuring maximal viability. BMI/age-adjusted dosing should be optimized to enhance outcomes. The Food and Drug Administration/ European Medicines Agency (FDA/EMA) treats autologous ADSCs as Human cells, tissues, and cellular and tissue-based products (HCT/Ps) or Advanced therapy medicinal products (ATMPs), which requires phase III data for a Biologics License Application (BLA) approval [201]. Also, Japan has the Pharmaceuticals and Medical Devices Agency (PMDA) approvals, which highlight conditional pathways for autologous use, and post-market surveillance tracks rare immunogenicity. Hence, the

clinical-grade ADSCs should obtain the respective approvals before clinical use.

9. Conclusion

The increasing aging population has contributed to a rapid increase in KOA incidence and exerted a healthcare burden. Besides, known/established factors like aging, gender, obesity, joint injury, genetic predisposition, the emerging risk factors such as diabetes mellitus, dyslipidemia, hypertension/blood pressure, gut microbiome dysbiosis, vitamin D deficiency, smoking, UPFs, biomechanical, and environmental pollutants for KOA should be extensively investigated. To date, surgical interventions are the last resort for curative treatment. However, the expenses, availability of surgical experts and facilities, and surgical complications related to aging limit their wide application. Notwithstanding, the stem cell-based tissue remodelling potential of OA remains an obvious choice for KOA treatment. Of them, the ADSCs and their derived exosome-based treatment, being minimally invasive, are considered one of the most promising, as demonstrated by the efficacy and safety in various clinical and pre-clinical studies. ADSCs not only promote cartilage regeneration but also inhibit inflammation and reduce pain, which may be further enhanced by synergistic administration of other therapeutic alternatives like PRP, SWT and XG, and HBO, etc. Thus, considering the role of ADSCs in inhibiting OA progression and treatment, more studies are required to explain molecular changes and to establish the standard clinical procedures for regenerative treatment.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

CHL conceived and designed the review. CHL, HTL, KTC, SHW, YFS, HHT, ACL, THK, and NKD conducted the literature search, formal analysis, and wrote the original draft. CHL, HTL, THK, and NKD participated in preparing figures. CHL, THK, and NKD critically reviewed and edited the manuscript. All the authors read and approved the final manuscript.

References

[1] Trombini-Souza F, Kimura A, Ribeiro AP, Butugan M, Akashi P, Pássaro AC, et al. (2011). Inexpensive footwear decreases joint loading in elderly women with knee osteoarthritis. Gait Posture, 34:126-130.

[2] Dubey NK, Wei HJ, Yu SH, Williams DF, Wang JR, Deng YH, et al. (2019). Adipose-derived Stem Cells Attenuates Diabetic Osteoarthritis via Inhibition of Glycation-mediated Inflammatory Cascade. Aging Dis, 10:483-496.

[3] Favero M, Ramonda R, Goldring MB, Goldring SR, Punzi L (2015). Early knee osteoarthritis. RMD Open, 1:e000062.

[4] Loeser RF, Goldring SR, Scanzello CR, Goldring MB (2012). Osteoarthritis: A disease of the joint as an organ. Arthritis & Rheumatism, 64:1697-1707.

[5] Cook CS, Smith PA (2018). Clinical Update: Why PRP Should Be Your First Choice for Injection Therapy in Treating Osteoarthritis of the Knee. Curr Rev Musculoskelet Med, 11:583-592.

[6] Fodor PB, Paulseth SG (2015). Adipose Derived Stromal Cell (ADSC) Injections for Pain Management of Osteoarthritis in the Human Knee Joint. Aesthetic Surgery Journal, 36:229-236.

[7] Felson DT (2006). Clinical practice. Osteoarthritis of the knee. N Engl J Med, 354:841-848.

[8] Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H (2020). Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine, 29-30:100587.

[9] Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT (2011). Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Ann Intern Med, 155:725-732.

[10] Ma L, Zheng X, Lin R, Sun AR, Song J, Ye Z, et al. (2022). Knee Osteoarthritis Therapy: Recent Advances in Intra-Articular Drug Delivery Systems. Drug Des Devel Ther, 16:1311-1347.

[11] Karnas E, Dudek P, Zuba-Surma EK (2023). Stem cell-derived extracellular vesicles as new tools in regenerative medicine - Immunomodulatory role and future perspectives. Frontiers in Immunology, 14.

[12] Maldonado VV, Patel NH, Smith EE, Barnes CL, Gustafson MP, Rao RR, et al. (2023). Clinical utility of mesenchymal stem/stromal cells in regenerative medicine and cellular therapy. Journal of Biological Engineering, 17:44.

[13] Arita A, Tobita M (2023). Current status of platelet-rich plasma therapy under the act on the safety of regenerative medicine in Japan. Regenerative Therapy, 23:37-43.

[14] Im G-I (2021). Current status of regenerative medicine in osteoarthritis. Bone & Joint Research, 10:134-136.

[15] Han Y, Li X, Zhang Y, Han Y, Chang F, Ding J (2019). Mesenchymal Stem Cells for Regenerative Medicine. Cells, 8.

[16] Gao F, Chiu SM, Motan DA, Zhang Z, Chen L, Ji HL, et al. (2016). Mesenchymal stem cells and immunomodulation: current status and future prospects. Cell Death Dis, 7:e2062.

[17] Frese L, Dijkman PE, Hoerstrup SP (2016). Adipose Tissue-Derived Stem Cells in Regenerative Medicine. Transfusion Medicine and Hemotherapy, 43:268-274.

[18] Berebichez-Fridman R, Montero-Olvera PR (2018). Sources and Clinical Applications of Mesenchymal

Stem Cells: State-of-the-art review. Sultan Qaboos Univ Med J, 18:e264-e277.

[19] Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, Gangadaran P, Rajendran RL, et al. (2023). Comparative effectiveness of adipose-derived mesenchymal stromal cells in the management of knee osteoarthritis: A meta-analysis. World J Orthop, 14:23-41.

[20] Miana VV, González EAP (2018). Adipose tissue stem cells in regenerative medicine. Ecancermedicalscience, 12:822.

[21] Koobatian MT, Liang MS, Swartz DD, Andreadis ST (2015). Differential effects of culture senescence and mechanical stimulation on the proliferation and leiomyogenic differentiation of MSC from different sources: implications for engineering vascular grafts. Tissue Eng Part A, 21:1364-1375.

[22] Chen C, Chen C-S, Liu T-C (2024). Exploring the association between knee osteoarthritis outpatient visits and Asian dust storms: a time-series analysis. Scientific Reports, 14:22544.

[23] Primorac D, Molnar V, Rod E, Jeleč Ž, Čukelj F, Matišić V, et al. (2020). Knee Osteoarthritis: A Review of Pathogenesis and State-Of-The-Art Non-Operative Therapeutic Considerations. Genes, 11:854.

[24] Mora JC, Przkora R, Cruz-Almeida Y (2018). Knee osteoarthritis: pathophysiology and current treatment modalities. J Pain Res, 11:2189-2196.

[25] Hayes B, Kittelson A, Loyd B, Wellsandt E, Flug J, Stevens-Lapsley J (2016). Assessing Radiographic Knee Osteoarthritis: An Online Training Tutorial for the Kellgren-Lawrence Grading Scale. MedEdPORTAL, 12:10503.

[26] Kellgren JH, Lawrence J (1957). Radiological assessment of osteo-arthrosis. Annals of the rheumatic diseases, 16:494.

[27] Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP (2015). Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis and Cartilage, 23:507-515.

[28] Fatoye F, Wright JM, Yeowell G, Gebrye T (2020). Clinical and cost-effectiveness of physiotherapy interventions following total hip replacement: a systematic review and meta-analysis. Rheumatology International, 40:1385-1398.

[29] Lynskey SJ, Macaluso MJ, Gill SD, McGee SL, Page RS (2023). Biomarkers of Osteoarthritis—A Narrative Review on Causal Links with Metabolic Syndrome. Life, 13:730.

[30] Rhon DI, Perez KG, Eskridge SL (2019). Risk of post-traumatic knee osteoarthritis after knee injury in military service members. Musculoskeletal Care, 17:113-119.

[31] He Q, Luo H, Mei J, Wang Z, Sun X, Wang L, et al. (2024). The association between accelerated biological aging and the risk of osteoarthritis: a cross-sectional study. Frontiers in Public Health, Volume 12 - 2024.

[32] Daniel RA, Kalaivani M, Aggarwal P, Gupta SK (2025). Prevalence of knee osteoarthritis among elderly persons in India: A systematic review and meta-analysis. J Family Med Prim Care, 14:1675-1684.

[33] Dong Y, Yan Y, Zhou J, Zhou Q, Wei H (2023). Evidence on risk factors for knee osteoarthritis in middle-older aged: a systematic review and meta analysis. J Orthop Surg Res, 18:634.

[34] Szilagyi IA, Waarsing JH, Schiphof D, van Meurs JBJ, Bierma-Zeinstra SMA (2021). Towards sex-specific osteoarthritis risk models: evaluation of risk factors for knee osteoarthritis in males and females. Rheumatology, 61:648-657.

[35] Segal NA, Nilges JM, Oo WM (2024). Sex differences in osteoarthritis prevalence, pain perception, physical function and therapeutics. Osteoarthritis and Cartilage, 32:1045-1053.

[36] Glass N, Segal NA, Sluka KA, Torner JC, Nevitt MC, Felson DT, et al. (2014). Examining sex differences in knee pain: the multicenter osteoarthritis study. Osteoarthritis Cartilage, 22:1100-1106.

[37] Chhabra A, Zijerdi D, Zhang J, Kline A, Balian G, Hurwitz S (2005). BMP-14 deficiency inhibits long bone fracture healing: a biochemical, histologic, and radiographic assessment. J Orthop Trauma, 19:629-634.

[38] Zhang C LH, SongJH, Yoon JW, Park YK, Nam SW, Lee JY, Park WS (2010). Growth Differentiation Factor 5 (GDF5) Core Promoter Polymorphism Is Not Associated with Susceptibility to Osteoarthritis of the Knee in the Korean Population. Journal of Pathology and Translational Medicine 44:404-409.

[39] Tsezou A, Satra M, Oikonomou P, Bargiotas K, Malizos KN (2008). The growth differentiation factor 5 (GDF5) core promoter polymorphism is not associated with knee osteoarthritis in the Greek population. J Orthop Res, 26:136-140.

[40] Gálvez-Rosas A, González-Huerta C, Borgonio-Cuadra VM, Duarte-Salazár C, Lara-Alvarado L, de los Ángeles Soria-Bastida M, et al. (2010). A COL2A1 gene polymorphism is related with advanced stages of osteoarthritis of the knee in Mexican Mestizo population. Rheumatology International, 30:1035-1039.

[41] Kaliakatsos M, Tzetis M, Kanavakis E, Fytili P, Chouliaras G, Karachalios T, et al. (2006). Asporin and knee osteoarthritis in patients of Greek origin. Osteoarthritis and Cartilage, 14:609-611.

[42] Sedaghati-Khayat B, Boer CG, Runhaar J, Bierma-Zeinstra SMA, Broer L, Ikram MA, et al. (2022). Risk Assessment for Hip and Knee Osteoarthritis Using Polygenic Risk Scores. Arthritis Rheumatol, 74:1488-1496.

[43] Morita Y, Kamatani Y, Ito H, Ikegawa S, Kawaguchi T, Kawaguchi S, et al. (2023). Improved genetic prediction of the risk of knee osteoarthritis using the risk factor-based polygenic score. Arthritis Res Ther, 25:103.

[44] Shumnalieva R, Kotov G, Monov S (2023). Obesity-Related Knee Osteoarthritis-Current Concepts. Life (Basel), 13.

[45] Mastbergen SC, Ooms A, Turmezei TD, MacKay JW, Van Heerwaarden RJ, Spruijt S, et al. (2022). Subchondral bone changes after joint distraction treatment for end stage knee osteoarthritis. Osteoarthritis Cartilage, 30:965-972.

[46] Heidari B (2011). Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. Caspian J Intern Med, 2:205-212.

[47] Iannone F, Lapadula G (2010). Obesity and inflammation-targets for OA therapy. Current drug targets, 11:586-598.

[48] Nguyen U-SD, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT (2011). Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Annals of internal medicine, 155:725-732.

[49] Linde KN, Puhakka KB, Langdahl BL, Søballe K, Krog-Mikkelsen I, Madsen F, et al. (2017). Bone Mineral Density is Lower in Patients with Severe Knee Osteoarthritis and Attrition. Calcified Tissue International, 101:593-601.

[50] Nevitt MC, Felson DT (2020). High bone density and radiographic osteoarthritis: questions answered and unanswered. Osteoarthritis Cartilage, 28:1151-1153.

[51] Wang L-J, Zeng N, Yan Z-P, Li J-T, Ni G-X (2020). Post-traumatic osteoarthritis following ACL injury. Arthritis Research & Therapy, 22:57.

[52] Wang X, Perry TA, Arden N, Chen L, Parsons CM, Cooper C, et al. (2020). Occupational Risk in Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Observational Studies. Arthritis Care Res (Hoboken), 72:1213-1223.

[53] Klussmann A, Gebhardt H, Nübling M, Liebers F, Quirós Perea E, Cordier W, et al. (2010). Individual and occupational risk factors for knee osteoarthritis: results of a case-control study in Germany. Arthritis Res Ther, 12:R88.

[54] Dubey NK, Wei H-J, Yu S-H, Williams DF, Wang JR, Deng Y-H, et al. (2019). Adipose-derived Stem Cells Attenuates Diabetic Osteoarthritis via Inhibition of Glycation-mediated Inflammatory Cascade. Aging and disease, 10:483-496.

[55] Dubey NK, Ningrum DNA, Dubey R, Deng YH, Li YC, Wang PD, et al. (2018). Correlation between Diabetes Mellitus and Knee Osteoarthritis: A Dry-To-Wet Lab Approach. Int J Mol Sci, 19.

[56] Eitner A, Rutte V, Marintschev I, Hofmann GO, Schaible H-G (2024). Enhanced joint pain in diabetic patients with knee osteoarthritis is associated with increased synovitis, synovial immune cell infiltration, and erythrocyte extravasation. Frontiers in Endocrinology, Volume 15 - 2024.

[57] Eitner A, Culvenor AG, Wirth W, Schaible H-G, Eckstein F (2021). Impact of Diabetes Mellitus on Knee Osteoarthritis Pain and Physical and Mental Status: Data From the Osteoarthritis Initiative. Arthritis Care & Research, 73:540-548.

[58] Hao K, Wang J, Niu Y, Wang F (2024). Obesity and hyperlipidemia were associated with more severe synovitis and structural abnormalities as well as inferior functional outcomes in knee osteoarthritis: a retrospective comparative study. Journal of Orthopaedic Surgery and Research, 19:845.

[59] Choi BS, Han H-S (2025). Dyslipidemia is Associated with an Increased Risk of Knee Osteoarthritis Regardless of Obesity: An Analysis of a Nationwide South Korean Cohort. Osteoarthritis and Cartilage, 33:S234.

[60] de Munter W, van den Bosch MH, Slöetjes AW, Croce KJ, Vogl T, Roth J, et al. (2016). High LDL levels lead to increased synovial inflammation and accelerated ectopic bone formation during experimental osteoarthritis. Osteoarthritis and Cartilage, 24:844-855.

[61] Lee JS, Kim YH, Jhun J, Na HS, Um IG, Choi JW, et al. (2024). Oxidized LDL Accelerates Cartilage Destruction and Inflammatory Chondrocyte Death in Osteoarthritis by Disrupting the TFEB-Regulated Autophagy-Lysosome Pathway. Immune Netw, 24.

[62] Ashmeik W, Joseph GB, Nevitt MC, Lane NE, McCulloch CE, Link TM (2020). Association of blood pressure with knee cartilage composition and structural knee abnormalities: data from the osteoarthritis initiative. Skeletal Radiol, 49:1359-1368.

[63] Lo K, Au M, Ni J, Wen C (2022). Association between hypertension and osteoarthritis: A systematic review and meta-analysis of observational studies. J Orthop Translat, 32:12-20.

[64] Boer CG, Radjabzadeh D, Medina-Gomez C, Garmaeva S, Schiphof D, Arp P, et al. (2019). Intestinal microbiome composition and its relation to joint pain and inflammation. Nat Commun, 10:4881.

[65] Gilat R, Yazdi AA, Weissman AC, Joyce KM, Bouftas FA, Muth SA, et al. (2025). The Gut Microbiome and Joint Microbiome Show Alterations in Patients With Knee Osteoarthritis Versus Controls: A Systematic Review. Arthroscopy, 41:1226-1238.

[66] Gaspar MG, Núñez-Carro C, Blanco-Blanco M, Blanco FJ, de Andrés MC (2025). Inflammaging contributes to osteoarthritis development and human microbiota variations and vice versa: A systematic review. Osteoarthritis and Cartilage, 33:218-230.

[67] Gleason B, Chisari E, Parvizi J (2022). Osteoarthritis Can Also Start in the Gut: The Gut-Joint Axis. Indian J Orthop, 56:1150-1155.

[68] Pesesse L, Sanchez C, Henrotin Y (2011). Osteochondral plate angiogenesis: a new treatment target in osteoarthritis. Joint Bone Spine, 78:144-149.

[69] Pesesse L, Sanchez C, Delcour JP, Bellahcène A, Baudouin C, Msika P, et al. (2013). Consequences of chondrocyte hypertrophy on osteoarthritic cartilage: potential effect on angiogenesis. Osteoarthritis Cartilage, 21:1913-1923.

[70] Zuo A, Jia Q, Zhang M, Zhou X, Li T, Wang L (2024). The association of vitamin D with knee osteoarthritis pain: an analysis from the Osteoarthritis Initiative database. Scientific Reports, 14:30176.

[71] Annamalai R, Sujhithra A, Danis Vijay D (2023). Association between vitamin D and knee osteoarthritis in Indian population: A systematic review and meta-analysis. Journal of Clinical Orthopaedics and Trauma, 46:102278.

[72] Busa P, Huang N, Kuthati Y, Wong C-S (2023). Vitamin D reduces pain and cartilage destruction in knee osteoarthritis animals through inhibiting the matrix metalloprotease (MMPs) expression. Heliyon, 9:e15268.

[73] Zhu S, Ji L, He Z, Zhang W, Tong Y, Luo J, et al. (2023). Association of smoking and osteoarthritis in US (NHANES 1999–2018). Scientific Reports, 13:3911.

[74] Felson DT, Zhang Y (2015). Smoking and osteoarthritis: a review of the evidence and its implications. Osteoarthritis Cartilage, 23:331-333.

[75] Salis Z, Sainsbury A (2024). Association of smoking with knee osteoarthritis structural defects and symptoms: an individual participant data meta-analysis. Scientific Reports, 14:29021.

[76] Amin S, Niu J, Guermazi A, Grigoryan M, Hunter DJ, Clancy M, et al. (2007). Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. Ann Rheum Dis, 66:18-22.

[77] Park J, Son M, Lee SY, Chung WT, Lee SW (2024). The relationship between tobacco smoking and knee osteoarthritis in regard of its incidence and progression: 10-year retrospective cohort study based on Korea National Health Insurance Service-Health Screening database. Osteoarthritis and Cartilage, 32:795-796.

[78] Akkaya Z, Sims WM, Lynch JA, Löffler MT, Gassert F, Nevitt M, et al. (2025). Ultra-processed food consumption is associated with knee osteoarthritis: Data from the Osteoarthritis Initiative. Osteoarthritis and Cartilage, 33:1130-1140.

[79] Sun W, Liu J, Steele EM, Yang X, Gao R, Wang C, et al. (2024). Association of ultra-processed food consumption with muscle mass among young and middle-aged US adults. Eur J Nutr, 63:2621-2629.

[80] Wei Y, Zhang T, Liu Y, Liu H, Zhou Y, Su J, et al. (2024). Ultra-processed food consumption, genetic susceptibility, and the risk of hip/knee osteoarthritis. Clin Nutr, 43:1363-1371.

[81] Abo-Elmaaty RM A-RR, Fekry ABH, El-Dakroory SBA, El-Harouny MA (2017). The correlation between blood lead levels and knee osteoarthritis: a preliminary Egyptian study. International Journal of Clinical Rheumatology, 12:083-090.

[82] Nelson AE, Shi XA, Schwartz TA, Chen JC, Renner JB, Caldwell KL, et al. (2011). Whole blood lead levels are associated with radiographic and symptomatic knee osteoarthritis: a cross-sectional analysis in the Johnston County Osteoarthritis Project. Arthritis Res Ther, 13:R37.

[83] Holz JD, Beier E, Sheu TJ, Ubayawardena R, Wang M, Sampson ER, et al. (2012). Lead induces an osteoarthritis-like phenotype in articular chondrocytes through disruption of TGF-β signaling. J Orthop Res, 30:1760-1766.

[84] Feng Z, Sun L, Niu S, Liu B, Ba R, Wang G, et al. (2025). Fluoride exposure, personal susceptibility and osteoarticular degeneration: Evidence from farmers in the Yellow River Basin of Henan Province. Ecotoxicology and Environmental Safety, 289:117435.

[85] Mohammad A CD (2022). PCBs and Dioxins Either Cause or Make Worse Both Osteo and Rheumatoid Arthritis. Medical Research Archives, 10.

[86] Shao W, Hou H, Han Q, Cai K (2024). Prevalence and risk factors of knee osteoarthritis: a cross-sectional survey in Nanjing, China. Frontiers in Public Health, Volume 12 - 2024.

[87] Iijima H, Ohi H, Isho T, Aoyama T, Fukutani N, Kaneda E, et al. (2017). Association of bilateral flat feet with knee pain and disability in patients with knee osteoarthritis: A cross-sectional study. J Orthop Res, 35:2490-2498.

[88] Schwartz I, Ofran Y, Bernovsky S, Kandel L, Rivkin G, Karniel N, et al. (2023). Cushioned Footwear Effect on Pain and Gait Characteristics of Individuals with Knee Osteoarthritis: A Double-Blinded 3 Month Intervention Study. Sensors, 23:1375.

[89] Jang S, Lee K, Ju JH (2021). Recent updates of diagnosis, pathophysiology, and treatment on osteoarthritis of the knee. International journal of molecular sciences, 22:2619.

[90] Kan H, Chan P, Chiu K, Yan C, Yeung S, Ng Y, et al. (2019). Non-surgical treatment of knee osteoarthritis. Hong Kong Medical Journal.

[91] Oo WM, Hunter J (2023). Intra-articular Therapies for Knee Osteoarthritis: Current Update. Current Treatment Options in Rheumatology, 9:99-119.

[92] Ayhan E, Kesmezacar H, Akgun I (2014). Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World journal of orthopedics, 5:351.

[93] Richards MM, Maxwell JS, Weng L, Angelos MG, Golzarian J (2016). Intra-articular treatment of knee osteoarthritis: from anti-inflammatories to products of regenerative medicine. The Physician and sportsmedicine, 44:101-108.

[94] Zeng C, Doherty M, Persson MSM, Yang Z, Sarmanova A, Zhang Y, et al. (2021). Comparative efficacy and safety of acetaminophen, topical and oral non-steroidal anti-inflammatory drugs for knee osteoarthritis: evidence from a network meta-analysis of randomized controlled trials and real-world data. Osteoarthritis and Cartilage, 29:1242-1251.

[95] Yu L, Luo R, Qin G, Zhang Q, Liang W (2023). Efficacy and safety of anti-interleukin-1 therapeutics in the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Journal of Orthopaedic Surgery and Research, 18:100.

[96] Cao Z, Zhou J, Long Z, Li Y, Sun J, Luo Y, et al. (2020). Targeting nerve growth factor, a new option for treatment of osteoarthritis: a network meta-analysis of comparative efficacy and safety with traditional drugs. Aging (Albany NY), 13:1051-1070.

[97] Ferkel E, Manjoo A, Martins D, Bhandari M, Sethi P, Nicholls M (2023). Intra-articular Hyaluronic Acid Treatments for Knee Osteoarthritis: A Systematic Review of Product Properties. Cartilage, 14:424-432.

[98] Reginster JY, Neuprez A, Lecart MP, Sarlet N, Bruyere O (2012). Role of glucosamine in the treatment for osteoarthritis. Rheumatol Int, 32:2959-2967.

[99] Messier SP (2010). Diet and exercise for obese adults with knee osteoarthritis. Clin Geriatr Med, 26:461-477.
[100] Jang S, Lee K, Ju JH (2021). Recent Updates of Diagnosis, Pathophysiology, and Treatment on Osteoarthritis of the Knee. Int J Mol Sci, 22.
[101] Rönn K, Reischl N, Gautier E, Jacobi M (2011). Current surgical treatment of knee osteoarthritis. Arthritis, 2011:454873.
[102] Tom GHW, Marinus W, Noortje ACVdB, Hidde JH, Maarten HM (2021). Autologous stem cell therapy in knee osteoarthritis: a systematic review of randomised controlled trials. British Journal of Sports Medicine, 55:1161.
[103] Le H, Xu W, Zhuang X, Chang F, Wang Y, Ding J (2020). Mesenchymal stem cells for cartilage regeneration. Journal of Tissue Engineering, 11:2041731420943839.
[104] Arshi A, Petrigliano FA, Williams RJ, Jones KJ (2020). Stem Cell Treatment for Knee Articular Cartilage Defects and Osteoarthritis. Curr Rev Musculoskelet Med, 13:20-27.
[105] Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grøntvedt T, Solheim E, et al. (2004). Autologous chondrocyte implantation compared with microfracture in the knee: a randomized trial. JBJS, 86:455-464.
[106] Samsudin EZ, Kamarul T (2016). The comparison between the different generations of autologous chondrocyte implantation with other treatment modalities: a systematic review of clinical trials. Knee Surgery, Sports Traumatology, Arthroscopy, 24:3912-3926.
[107] Davies RL, Kuiper NJ (2019). Regenerative medicine: a review of the evolution of autologous chondrocyte implantation (ACI) therapy. Bioengineering, 6:22.
[108] Pareek A, Carey JL, Reardon PJ, Peterson L, Stuart MJ, Krych AJ (2016). Long-Term Outcomes after Autologous Chondrocyte Implantation: A Systematic Review at Mean Follow-Up of 11.4 Years. Cartilage, 7:298-308.
[109] Ntege EH, Sunami H, Shimizu Y (2020). Advances in regenerative therapy: A review of the literature and future directions. Regen Ther, 14:136-153.
[110] Freitag J, Bates D, Wickham J, Shah K, Huguenin L, Tenen A, et al. (2019). Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. Regenerative Medicine, 14:213-230.
[111] Doss MX, Sachinidis A (2019). Current Challenges of iPSC-Based Disease Modeling and Therapeutic Implications. Cells, 8.
[112] Huang CY, Liu CL, Ting CY, Chiu YT, Cheng YC, Nicholson MW, et al. (2019). Human iPSC banking: barriers and opportunities. J Biomed Sci, 26:87.
[113] Mahla RS (2016). Stem Cells Applications in Regenerative Medicine and Disease Therapeutics. Int J Cell Biol, 2016:6940283.
[114] Dai R, Wang Z, Samanipour R, Koo KI, Kim K (2016). Adipose-Derived Stem Cells for Tissue Engineering and Regenerative Medicine Applications. Stem Cells Int, 2016:6737345.
[115] Zhang J, Liu Y, Chen Y, Yuan L, Liu H, Wang J, et al. (2020). Adipose-Derived Stem Cells: Current Applications and Future Directions in the Regeneration of Multiple Tissues. Stem Cells International, 2020:8810813.
[116] Al-Ghadban S, Artiles M, Bunnell BA (2022). Adipose Stem Cells in Regenerative Medicine: Looking Forward. Frontiers in Bioengineering and Biotechnology, 9.
[117] Mukhamedshina Y, Shulman I, Ogurcov S, Kostennikov A, Zakirova E, Akhmetzyanova E, et al. (2019). Mesenchymal stem cell therapy for spinal cord contusion: a comparative study on small and large animal models. Biomolecules, 9:811.
[118] Lu L, Dai C, Zhang Z, Du H, Li S, Ye P, et al. (2019). Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. Stem cell research & therapy, 10:1-10.
[119] Zhang X, Guo J, Zhou Y, Wu G (2014). The roles of bone morphogenetic proteins and their signaling in the osteogenesis of adipose-derived stem cells. Tissue Engineering Part B: Reviews, 20:84-92.
[120] Qin Y, Ge G, Yang P, Wang L, Qiao Y, Pan G, et al. (2023). An Update on Adipose-Derived Stem Cells for Regenerative Medicine: Where Challenge Meets Opportunity. Advanced Science, 10:2207334.
[121] Simonacci F, Bertozzi N, Grieco MP, Raposio E (2019). From liposuction to adipose-derived stem cells: indications and technique. Acta Biomed, 90:197-208.
[122] Khazaei S, Keshavarz G, Bozorgi A, Nazari H, Khazaei M (2022). Adipose tissue-derived stem cells: a comparative review on isolation, culture, and differentiation methods. Cell and Tissue Banking, 23:1-16.
[123] Lapuente JP, Dos-Anjos S, Blázquez-Martínez A (2020). Intra-articular infiltration of adipose-derived stromal vascular fraction cells slows the clinical progression of moderate-severe knee osteoarthritis: hypothesis on the regulatory role of intra-articular adipose tissue. Journal of Orthopaedic Surgery and Research, 15:137.
[124] Kim YS, Oh SM, Suh DS, Tak DH, Kwon YB, Koh YG (2023). Cartilage lesion size and number of stromal vascular fraction (SVF) cells strongly influenced the SVF implantation outcomes in patients with knee osteoarthritis. J Exp Orthop, 10:28.
[125] Van Pham P, Vu NB, Phan NL-C, Le DM, Truong NC, Truong NH, et al. (2014). Good manufacturing practice-compliant isolation and culture of human adipose derived stem cells. Biomedical Research and Therapy, 1:21.
[126] Chun SY, Lim JO, Lee EH, Han MH, Ha YS, Lee JN, et al. (2019). Preparation and Characterization of Human Adipose Tissue-Derived Extracellular Matrix, Growth Factors, and Stem Cells: A Concise Review. Tissue Eng Regen Med, 16:385-393.
[127] Gentile P, Piccinno MS, Calabrese C (2019). Characteristics and potentiality of human adipose-

derived stem cells (hASCs) obtained from enzymatic digestion of fat graft. Cells, 8:282.

[128] Matsuo Y, Morita H, Yamagishi H, Nakamura M, Takeshima Y, Nakagawa I, et al. (2021). Isolation of adipose tissue-derived stem cells by direct membrane migration and expansion for clinical application. Human Cell, 34:819-824.

[129] Chen C-F, Hu C-C, Wu C-T, Wu H-TH, Chang C-S, Hung Y-P, et al. (2021). Treatment of knee osteoarthritis with intra-articular injection of allogeneic adipose-derived stem cells (ADSCs) ELIXCYTE®: a phase I/II, randomized, active-control, single-blind, multiple-center clinical trial. Stem Cell Research & Therapy, 12:562.

[130] Van Pham P, Bui KH-T, Duong TD, Nguyen NT, Nguyen TD, Le VT, et al. (2014). Symptomatic knee osteoarthritis treatment using autologous adipose derived stem cells and platelet-rich plasma: a clinical study. Biomedical Research and Therapy, 1:2.

[131] Hong Z, Chen J, Zhang S, Zhao C, Bi M, Chen X, et al. (2019). Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial. International Orthopaedics, 43:1123-1134.

[132] Schiavone Panni A, Vasso M, Braile A, Toro G, De Cicco A, Viggiano D, et al. (2019). Preliminary results of autologous adipose-derived stem cells in early knee osteoarthritis: identification of a subpopulation with greater response. International Orthopaedics, 43:7-13.

[133] Sadri B, Hassanzadeh M, Bagherifard A, Mohammadi J, Alikhani M, Moeinabadi-Bidgoli K, et al. (2023). Cartilage regeneration and inflammation modulation in knee osteoarthritis following injection of allogeneic adipose-derived mesenchymal stromal cells: a phase II, triple-blinded, placebo controlled, randomized trial. Stem Cell Research & Therapy, 14:162.

[134] Yang W-T, Ke C-Y, Yeh K-T, Huang S-G, Lin Z-Y, Wu W-T, et al. (2022). Stromal-vascular fraction and adipose-derived stem cell therapies improve cartilage regeneration in osteoarthritis-induced rats. Scientific Reports, 12:2828.

[135] Kuroda K, Kabata T, Hayashi K, Maeda T, Kajino Y, Iwai S, et al. (2015). The paracrine effect of adipose-derived stem cells inhibits osteoarthritis progression. BMC Musculoskeletal Disorders, 16:236.

[136] Gonzalez-Fernandez P, Rodríguez-Nogales C, Jordan O, Allémann E (2022). Combination of mesenchymal stem cells and bioactive molecules in hydrogels for osteoarthritis treatment. European Journal of Pharmaceutics and Biopharmaceutics, 172:41-52.

[137] Epanomeritakis IE, Khan WS (2024). Adipose-derived regenerative therapies for the treatment of knee osteoarthritis. World J Stem Cells, 16:324-333.

[138] Liang W, Zhou C, Liu X, Xie Q, Xia L, Liu L, et al. (2025). Current status of nano-embedded growth factors and stem cells delivery to bone for targeted repair and regeneration. J Orthop Translat, 50:257-273.

[139] Sun Z, Fukui M, Taketani S, Kako A, Kunieda S, Kakudo N (2024). Predominant control of PDGF/PDGF receptor signaling in the migration and proliferation of human adipose-derived stem cells under culture conditions with a combination of growth factors. Exp Ther Med, 27:156.

[140] Du X, Cai L, Xie J, Zhou X (2023). The role of TGF-beta3 in cartilage development and osteoarthritis. Bone Research, 11:2.

[141] Chen G, Deng C, Li YP (2012). TGF-β and BMP signaling in osteoblast differentiation and bone formation. Int J Biol Sci, 8:272-288.

[142] Chen H-H, Chen Y-C, Yu S-N, Lai W-L, Shen Y-S, Shen P-C, et al. (2022). Infrapatellar fat pad-derived mesenchymal stromal cell product for treatment of knee osteoarthritis: a first-in-human study with evaluation of the potency marker. Cytotherapy, 24:72-85.

[143] Escobar Ivirico JL, Bhattacharjee M, Kuyinu E, Nair LS, Laurencin CT (2017). Regenerative Engineering for Knee Osteoarthritis Treatment: Biomaterials and Cell-Based Technologies. Engineering, 3:16-27.

[144] Wang S, Qiu Y, Qu L, Wang Q, Zhou Q (2022). Hydrogels for Treatment of Different Degrees of Osteoarthritis. Frontiers in Bioengineering and Biotechnology, 10.

[145] Im GI, Kim HJ, Lee JH (2011). Chondrogenesis of adipose stem cells in a porous PLGA scaffold impregnated with plasmid DNA containing SOX trio (SOX-5,-6 and -9) genes. Biomaterials, 32:4385-4392.

[146] Bhattacharjee M, Escobar Ivirico JL, Kan HM, Shah S, Otsuka T, Bordett R, et al. (2022). Injectable amnion hydrogel-mediated delivery of adipose-derived stem cells for osteoarthritis treatment. Proc Natl Acad Sci U S A, 119.

[147] Yu W, Hu B, Boakye-Yiadom KO, Ho W, Chen Q, Xu X, et al. (2021). Injectable hydrogel mediated delivery of gene-engineered adipose-derived stem cells for enhanced osteoarthritis treatment. Biomaterials Science, 9:7603-7616.

[148] Franklin SP, Stoker AM, Bozynski CC, Kuroki K, Clarke KM, Johnson JK, et al. (2018). Comparison of platelet-rich plasma, stromal vascular fraction (SVF), or SVF with an injectable PLGA nanofiber scaffold for the treatment of osteochondral injury in dogs. The Journal of Knee Surgery, 31:686-697.

[149] Şahin AA, Değirmenci E, Özturan KE, Fırat T, Kükner A (2021). Effects of adipose tissue-derived stromal vascular fraction on osteochondral defects treated by hyaluronic acid-based scaffold: An experimental study. Jt Dis Relat Surg, 32:347-354.

[150] Hsu Y-K, Sheu S-Y, Wang C-Y, Chuang M-H, Chung P-C, Luo Y-S, et al. (2018). The effect of adipose-derived mesenchymal stem cells and chondrocytes with platelet-rich fibrin releasates augmentation by intra-articular injection on acute osteochondral defects in a rabbit model. The Knee, 25:1181-1191.

[151] Takagi T, Kabata T, Hayashi K, Fang X, Kajino Y, Inoue D, et al. (2020). Periodic injections of adipose-derived stem cell sheets attenuate osteoarthritis progression in an experimental rabbit model. BMC Musculoskeletal Disorders, 21:691.

[152] Kato Y, Iwata T, Morikawa S, Yamato M, Okano T, Uchigata Y (2015). Allogeneic transplantation of an adipose-derived stem cell sheet combined with artificial skin accelerates wound healing in a rat wound model of type 2 diabetes and obesity. Diabetes, 64:2723-2734.

[153] Wei F, Qu C, Song T, Ding G, Fan Z, Liu D, et al. (2012). Vitamin C treatment promotes mesenchymal stem cell sheet formation and tissue regeneration by elevating telomerase activity. Journal of cellular physiology, 227:3216-3224.

[154] Yu J, Tu Y-K, Tang Y-B, Cheng N-C (2014). Stemness and transdifferentiation of adipose-derived stem cells using L-ascorbic acid 2-phosphate-induced cell sheet formation. Biomaterials, 35:3516-3526.

[155] Ishida O, Hagino I, Nagaya N, Shimizu T, Okano T, Sawa Y, et al. (2015). Adipose-derived stem cell sheet transplantation therapy in a porcine model of chronic heart failure. Translational Research, 165:631-639.

[156] Kimura M, Nakase J, Takata Y, Shimozaki K, Asai K, Yoshimizu R, et al. (2023). Regeneration Using Adipose-Derived Stem Cell Sheets in a Rabbit Meniscal Defect Model Improves Tensile Strength and Load Distribution Function of the Meniscus at 12 Weeks. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 39:360-370.

[157] Takata Y, Nakase J, Shimozaki K, Asai K, Tsuchiya H (2020). Autologous Adipose-Derived Stem Cell Sheet Has Meniscus Regeneration-Promoting Effects in a Rabbit Model. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 36:2698-2707.

[158] Taninaka A, Kabata T, Hayashi K, Kajino Y, Inoue D, Ohmori T, et al. (2023). Chondroprotective Effects of Chondrogenic Differentiated Adipose-Derived Mesenchymal Stem Cells Sheet on Degenerated Articular Cartilage in an Experimental Rabbit Model. Bioengineering, 10:574.

[159] An S, Li J, Xie W, Yin N, Li Y, Hu Y (2020). Extracorporeal shockwave treatment in knee osteoarthritis: therapeutic effects and possible mechanism. Biosci Rep, 40.

[160] Hsu CC, Cheng JH, Wang CJ, Ko JY, Hsu SL, Hsu TC (2020). Shockwave Therapy Combined with Autologous Adipose-Derived Mesenchymal Stem Cells Is Better than with Human Umbilical Cord Wharton's Jelly-Derived Mesenchymal Stem Cells on Knee Osteoarthritis. Int J Mol Sci, 21.

[161] Cheng JH, Yen KT, Chou WY, Jhan SW, Hsu SL, Ko JY, et al. (2021). Autologous Adipose-Derived Mesenchymal Stem Cells Combined with Shockwave Therapy Synergistically Ameliorates the Osteoarthritic Pathological Factors in Knee Joint. Pharmaceuticals (Basel), 14.

[162] Mei L, Shen B, Xue J, Liu S, Ma A, Liu F, et al. (2017). Adipose tissue–derived stem cells in combination with xanthan gum attenuate osteoarthritis progression in an experimental rat model. Biochemical and Biophysical Research Communications, 494:285-291.

[163] Kitajima H, Sakamoto T, Horie T, Kuwano A, Fuku A, Taki Y, et al. (2023). Synovial Fluid Derived from Human Knee Osteoarthritis Increases the Viability of Human Adipose-Derived Stem Cells through Upregulation of FOSL1. Cells, 12:330.

[164] Juskovic A, Nikolic M, Ljujic B, Matic A, Zivkovic V, Vucicevic K, et al. (2022). Effects of Combined Allogenic Adipose Stem Cells and Hyperbaric Oxygenation Treatment on Pathogenesis of Osteoarthritis in Knee Joint Induced by Monoiodoacetate. International Journal of Molecular Sciences, 23:7695.

[165] Koh Y-G, Kwon O-R, Kim Y-S, Choi Y-J (2014). Comparative Outcomes of Open-Wedge High Tibial Osteotomy With Platelet-Rich Plasma Alone or in Combination With Mesenchymal Stem Cell Treatment: A Prospective Study. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 30:1453-1460.

[166] Van Pham P, Bui KH-T, Ngo DQ, Vu NB, Truong NH, Phan NL-C, et al. (2013). Activated platelet-rich plasma improves adipose-derived stem cell transplantation efficiency in injured articular cartilage. Stem Cell Research & Therapy, 4:91.

[167] Ude CC, Shamsul BS, Ng MH, Chen HC, Ohnmar H, Amaramalar SN, et al. (2018). Long-term evaluation of osteoarthritis sheep knee, treated with TGF-β3 and BMP-6 induced multipotent stem cells. Experimental Gerontology, 104:43-51.

[168] Cao TS, Viet TN (2023). Evaluating the Effects on Ultrasound and on Magnetic Resonance for Knee Osteoarthritis Treatment by Platelet Rich Plasma Therapy in Combination with Mesenchymal Stem Cells from Autologous Adipose Tissue. Open Journal of Regenerative Medicine, 12:114-124.

[169] Hosono Y, Kuwasawa A, Toyoda E, Nihei K, Sato S, Watanabe M, et al. (2023). Multiple intra-articular injections with adipose-derived stem cells for knee osteoarthritis cause severe arthritis with anti-histone H2B antibody production. Regenerative Therapy, 24:147-153.

[170] Jeong S-Y, Kang M-L, Park J-W, Im G-I (2020). Dual functional nanoparticles containing SOX duo and ANGPT4 shRNA for osteoarthritis treatment. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 108:234-242.

[171] Di Bella MA (2022). Overview and Update on Extracellular Vesicles: Considerations on Exosomes and Their Application in Modern Medicine. Biology (Basel), 11.

[172] An Y, Zhao J, Nie F, Qin Z, Xue H, Wang G, et al. (2019). Exosomes from Adipose-Derived Stem Cells (ADSCs) Overexpressing miR-21 Promote Vascularization of Endothelial Cells. Scientific Reports, 9:12861.

[173] Nguyen TH, Pham PV, Vu NB (2023). Exosomes from adipose-derived stem cells promote angiogenesis and reduce necrotic grade in hindlimb ischemia mouse models. Iran J Basic Med Sci, 26:429-437.

[174] Huang LH, Rau CS, Wu SC, Wu YC, Wu CJ, Tsai CW, et al. (2021). Identification and characterization of hADSC-derived exosome proteins from different isolation methods. J Cell Mol Med, 25:7436-7450.

[175] Jeyaraman M, Muthu S, Gulati A, Jeyaraman N, GS P, Jain R (2021). Mesenchymal Stem Cell–Derived Exosomes: A Potential Therapeutic Avenue in Knee Osteoarthritis. Cartilage, 13:1572S-1585S.

[176] Tao SC, Yuan T, Zhang YL, Yin WJ, Guo SC, Zhang CQ (2017). Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue regeneration and prevent osteoarthritis of the knee in a rat model. Theranostics, 7:180-195.

[177] Cavallo C, Merli G, Borzì RM, Zini N, D'Adamo S, Guescini M, et al. (2021). Small Extracellular Vesicles from adipose derived stromal cells significantly attenuate in vitro the NF-κB dependent inflammatory/catabolic environment of osteoarthritis. Scientific Reports, 11:1053.

[178] Meng C, Na Y, Han C, Ren Y, Liu M, Ma P, et al. (2023). Exosomal miR-429 derived from adipose-derived stem cells ameliorated chondral injury in osteoarthritis via autophagy by targeting FEZ2. International Immunopharmacology, 120:110315.

[179] Zhao J, Sun Y, Sheng X, Xu J, Dai G, He R, et al. (2023). Hypoxia-treated adipose mesenchymal stem cell-derived exosomes attenuate lumbar facet joint osteoarthritis. Molecular Medicine, 29:120.

[180] Li C, Li W, Pu G, Wu J, Qin F (2022). Exosomes derived from miR-338-3p-modified adipose stem cells inhibited inflammation injury of chondrocytes via targeting RUNX2 in osteoarthritis. Journal of Orthopaedic Surgery and Research, 17:567.

[181] Li Y, Duan J, Lin W, Liu J (2023). Exosomal miR-93-5p regulated the progression of osteoarthritis by targeting ADAMTS9. Open Medicine, 18.

[182] Zhao C, Chen JY, Peng WM, Yuan B, Bi Q, Xu YJ (2020). Exosomes from adipose-derived stem cells promote chondrogenesis and suppress inflammation by upregulating miR-145 and miR-221. Mol Med Rep, 21:1881-1889.

[183] Wu J, Kuang L, Chen C, Yang J, Zeng W-N, Li T, et al. (2019). miR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR in osteoarthritis. Biomaterials, 206:87-100.

[184] Xie A, Xue J, Wang Y, Yang C, Xu M, Jiang Y (2022). Kartogenin Induced Adipose-Derived Stem Cell Exosomes Enhance the Chondrogenic Differentiation Ability of Adipose-Derived Stem Cells. Disease Markers, 2022:6943630.

[185] Li Q, Yu H, Sun M, Yang P, Hu X, Ao Y, et al. (2021). The tissue origin effect of extracellular vesicles on cartilage and bone regeneration. Acta Biomaterialia, 125:253-266.

[186] Zhao S, Xiu G, Wang J, Wen Y, Lu J, Wu B, et al. (2023). Engineering exosomes derived from subcutaneous fat MSCs specially promote cartilage repair as miR-199a-3p delivery vehicles in Osteoarthritis. Journal of Nanobiotechnology, 21:341.

[187] Lee JC, Choe SY (2020). Gene Alterations after Human Adipose-Derived Stem Cell-Derived Exosome Injection in Monosodium Iodoacetate-Induced Osteoarthritis Rats by Microarray Analysis. Journal of the Anatomical Society of India, 69.

[188] Li R, Li D, Wang H, Chen K, Wang S, Xu J, et al. (2022). Exosomes from adipose-derived stem cells regulate M1/M2 macrophage phenotypic polarization to promote bone healing via miR-451a/MIF. Stem Cell Research & Therapy, 13:149.

[189] Li G, Zhang Y, Wu J, Yang R, Sun Q, Xu Y, et al. (2023). Adipose stem cells-derived exosomes modified gelatin sponge promotes bone regeneration. Frontiers in Bioengineering and Biotechnology, 11.

[190] Veronesi F, Berni M, Marchiori G, Cassiolas G, Muttini A, Barboni B, et al. (2021). Evaluation of cartilage biomechanics and knee joint microenvironment after different cell-based treatments in a sheep model of early osteoarthritis. International Orthopaedics, 45:427-435.

[191] Pintore A, Notarfrancesco D, Zara A, Oliviero A, Migliorini F, Oliva F, et al. (2023). Intra-articular injection of bone marrow aspirate concentrate (BMAC) or adipose-derived stem cells (ADSCs) for knee osteoarthritis: a prospective comparative clinical trial. Journal of Orthopaedic Surgery and Research, 18:350.

[192] Huang J, Liu Q, Xia J, Chen X, Xiong J, Yang L, et al. (2022). Modification of mesenchymal stem cells for cartilage-targeted therapy. Journal of Translational Medicine, 20:515.

[193] Brindo da Cruz IC, Velosa APP, Carrasco S, dos Santos Filho A, Tomaz de Miranda J, Pompeu E, et al. (2021). Post-Adipose-Derived Stem Cells (ADSC) Stimulated by Collagen Type V (Col V) Mitigate the Progression of Osteoarthritic Rabbit Articular Cartilage. Frontiers in Cell and Developmental Biology, 9.

[194] Yang Q, Jia L, Li X, Guo R, Huang Y, Zheng Y, et al. (2018). Long Noncoding RNAs: New Players in the Osteogenic Differentiation of Bone Marrow- and Adipose-Derived Mesenchymal Stem Cells. Stem Cell Rev Rep, 14:297-308.

[195] Pang HL, Zhao QQ, Ma Y, Song YL, Min J, Lu JR, et al. (2019). Long Noncoding RNA H19 Participates in the Regulation of Adipose-Derived Stem Cells Cartilage Differentiation. Stem Cells Int, 2019:2139814.

[196] Yang Q, Guo J, Ren Z, Li B, Huang H, Yang Z (2021). LncRNA NONHSAT030515 promotes the chondrogenic differentiation of human adipose-derived stem cells via regulating the miR-490-5p/BMPR2 axis. Journal of Orthopaedic Surgery and Research, 16:658.

[197] de Sousa EB, Gabbi Filho JPA, Gameiro VS, Baptista LS (2024). Adipose-derived stem cells and knee osteoarthritis: New perspectives, old concerns. World J Orthop, 15:1001-1006.

[198] Kim KI, Kim MS, Kim JH (2023). Intra-articular Injection of Autologous Adipose-Derived Stem Cells or Stromal Vascular Fractions: Are They Effective for Patients With Knee Osteoarthritis? A Systematic Review With Meta-analysis of Randomized Controlled Trials. Am J Sports Med, 51:837-848.

[199] Miller D, Grant A, Durgam S, El-Hayek K, Flanigan D, Malanga G, et al. (2021). Adipose-Derived Stem Cells, Obesity, and Inflammation: A Systematic Review and

Implications for Osteoarthritis Treatment. American Journal of Physical Medicine & Rehabilitation, Publish Ahead of Print.

[200] Pérez LM, Suárez J, Bernal A, de Lucas B, San Martin N, Gálvez BG (2016). Obesity-driven alterations in adipose-derived stem cells are partially restored by weight loss. Obesity, 24:661-669.

[201] Yano K, Watanabe N, Tsuyuki K, Ikawa T, Kasanuki H, Yamato M (2015). Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan. Regen Ther, 1:45-56.