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Current and novel theranostic modalities for knee osteoarthritis

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Abstract

Osteoarthritis is the second most common disorder after heart disease. This progressive degenerative disease affects the knee joint more than any others. The exact etiology of knee osteoarthritis is not clear, however, there are many predisposing factors such as obesity, age, gender, etc., that can increase the incidence and prevalence of this disease. Early diagnosis in knee osteoarthritis is very important. Despite the variety of diagnostic methods, lack of a valid and reliable diagnostic approach to detect the disorder in early stages has always been a challenge for researchers. Establishing an efficient therapeutic protocol for these patients is another crucial challenge. Recently, in addition to conventional treatments, which are surgical and non-surgical, tissue engineering and regenerative medicine as novel therapeutic modalities have received remarkable attention. In this paper, current diagnostic and therapeutic methods for knee osteoarthritis are discussed and potential biomarkers for early diagnosis and monitoring the clinical condition are discussed.

Keywords: knee osteoarthritis; cartilage regeneration; tissue engineering; stem cell therapy; biomarkers; mesenchymal stromal cells; regenerative medicine

MeSH terms:

OSTEOARTHRITIS, KNEE – DIAGNOSIS

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Традиционные и новые методы лечения остеоартрита коленного сустава с использованием тераностического подхода

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Аннотация

Остеоартрит – второе по распространенности заболевание после болезней сердечно-сосудистой системы. Это прогрессирующее дегенеративное заболевание поражает в большей степени коленный сустав. Точная этиология остеоартрита коленного сустава не ясна, однако существует множество предрасполагающих факторов, таких как ожирение, возраст, пол и другие, которые могут увеличить заболеваемость и распространенность этого заболевания. Очень важна ранняя диагностика остеоартрита коленного сустава. Несмотря на разнообразие диагностических методов, отсутствие надежного диагностического подхода для выявления расстройства на ранних стадиях всегда было проблемой для исследователей. Еще одной важной задачей является создание эффективного терапевтического протокола для этих пациентов. В последнее время, в дополнение к традиционным хирургическим и нехирургическим методам лечения, применяются методики тканевой инженерии и регенеративной медицины в качестве новых терапевтических методов, представляющих значительный интерес. В этой статье обсуждаются современные методы диагностики и лечения остеоартрита коленного сустава, а также обсуждаются потенциальные биомаркеры для ранней диагностики и мониторинга клинического состояния.

Ключевые слова: остеоартрит коленного сустава; регенерация суставного хряща; тканевая инженерия; терапия стволовыми клетками; биомаркеры; мезенхимальные стромальные клетки; регенеративная медицина

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List of abbreviation

OA – osteoarthritis
 KOA – knee osteoarthritis
 MRI – magnetic resonance imaging
 WOMAC – Western Ontario and McMaster Universities
 Osteoarthritis Index
 KOOS – knee injury and osteoarthritis outcome score

HA – hyaluronic acid
 NSAIDs – non-steroidal anti-inflammatory drugs
 UKA – Uni-compartmental knee arthroplasty
 TKA – total knee arthroplasty
 MSCs – mesenchymal stromal cells
 PRP – platelet-rich plasma

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
Osteoarthritis is the most common joint disease.	Остеоартрит – наиболее частое заболевание суставов.
Lack of blood supply, limited nutrition, and constant mechanical pressure applied to the joints lead osteoarthritis to be a progressive disease.	К прогрессированию остеоартрита приводят трофические нарушения и механическое воздействие на сустав.
Epidemiological studies show that knee joint is exposed to the risk of osteoarthritis more than the other joints.	По данным эпидемиологических исследований, наиболее часто риску развития остеоартрита подвержен коленный сустав.
Disruption of the physiological balance between anabolic and catabolic activity of the chondrocytes can be identified as the etiology of knee osteoarthritis.	В качестве причины остеоартрита коленного сустава рассматривается нарушение физиологического баланса между анаболической и катаболической активностью хондроцитов.
The entire joint structure such as subchondral bones, meniscus, ligaments and etc. could be affected by knee osteoarthritis.	При остеоартрите коленного сустава поражаются все структуры сустава, такие как субхондральная кость, мениск, связки и другие.
Local and systemic evaluation of the biomarkers can be useful in the early diagnosis of the knee osteoarthritis.	Для ранней диагностики остеоартрита коленного сустава может использоваться определение биомаркеров в крови и синовиальной жидкости.
Regenerative and immunomodulatory characteristics of mesenchymal stromal cells have made them a preferred cell source in cartilage tissue engineering.	Регенеративные и иммуномодулирующие особенности мезенхимальных стромальных клеток сделали их предпочтительным источником клеток в тканевой инженерии хрящевой ткани.
Cell-based scaffold-free therapies not only accelerates the cartilage repairs but also reduces the need for surgery and the complications of scaffold implantation.	Клеточная терапия без использования каркасов не только ускоряет восстановление хряща, но также снижает потребность в хирургическом вмешательстве и снижает количество осложнений при имплантации каркаса.

Osteoarthritis (OA) is the most common joint disease that can lead to disability and pain in patients and affect their quality of life [1]. The most important feature of OA is the articular cartilage degeneration [2].

Due to the lack of blood supply, limited nutrition, and constant mechanical pressure applied to the tissue which disrupts the balance between the anabolic and catabolic pathways, the ability of spontaneous cartilage repair is reduced [3]. This disorder is reported in different joints such as knee, hip, spine, etc. which bear weight. According to epidemiological studies, knee osteoarthritis (KOA) is the most common type of OA [4, 5]. Primary, with the emergence of KOA, femoral and tibial cartilage gradually degrade and subsequently lead to patellar cartilage involvement and injury [6]. The incidence and prevalence of this disease cannot be attributed to a specific etiology or mechanism. Therefore, complicated interactions between metabolic, genetic, mechanical and biochemical factors have always been suggested as a leading factor in the initiation and progression of this disease [7, 8]. In addition, local factors such as trauma, obesity, and hypermobility of the joint can contribute to the progression of KOA [9]. Although the etiology of the disease has not been clearly established, clinical studies

have shown that obese and elderly people and women are more exposed to KOA [10, 11].

Pain, stiffness, swelling, effusion, crepitus, joint weakness, limitation in movement, sensitivity to cold, and decreased function have known as clinical symptoms of KOA that all or some of them are reported by patients. Pain as one of the main symptoms of KOA has been seen in most patients and due to the reciprocity of changes in cartilage, bones remodeling, osteophytes formation, and inflammation caused by cartilage destruction [12]. To assess clinical symptoms, the use of diagnostic equipment for diagnosis and monitoring the progression of KOA is common. One of the main diagnostic methods is radiography. In addition to radiography, other imaging-based systems such as magnetic resonance imaging (MRI), computed tomography scan, arthroscopy and nuclear medicine-based techniques have been used to detect KOA related changes [13]. Despite different diagnostic methods, it is difficult to diagnose OA in the early stages. In this regard, the evaluation of specific biomarkers in physiological fluids has been proposed as a diagnostic method for early diagnosis.

Despite of the various therapeutic approaches, finding a definitive cure for KOA remains a concern

for researchers and physicians. Most of the current therapeutic methods that have been used to prevent further damage, can only reduce the pain. In general, conventional treatments for KOA are classified into two major categories: surgical and non-surgical therapies [14]. Non-surgical treatments – including pharmacological and non-pharmacological approaches, have been recommended by American College of Rheumatology (ACR) as the first line treatments for KOA [15]. If the first line treatments were not effective, particularly in patients with higher grade of KOA, surgical treatments will be recommended for the patients [16]. Although these therapies are still widely used for the treatment of KOA, in recent years biological treatments such as cell therapy and tissue engineering have received great attention [17, 18]. The purpose of this review article is to evaluate the epidemiology and etiology of KOA and to explain current therapeutic and diagnostic methods.

EPIDEMIOLOGY

KOA is one of the prevalent types of OA worldwide, especially in developed countries. According to an epidemiological study in Norway, KOA with 7.1% prevalence was the most common type of arthritis compared to hip and hand arthritis with 5.5% and 4.3%, respectively [19]. Furthermore, in a systemic analysis that evaluated global burden of 289 diseases between 1990 to 2010, KOA was considered for 83% of OA burden [20]. In addition, the evaluation of patients with KOA in terms of age, gender and place of residence, provides meaningful information on the choice of appropriate treatment methods and also prevention of disease.

The results of these studies have shown that among the young, the rate of KOA is significantly low and mainly caused by trauma. While, among 50-year-old people or elder, KOA has been known as the main cause of knee pain [21, 22]. KOA among individuals elder than 50 years old has doubled since the mid-20th century [23]. Moreover, females are exposed more than males, generally. According to a study in US, 6.1 million people suffered from KOA who were 45 to 64 years old. The total number of 3.6 million women and 2.5 million men were registered in this study. Also, in the evaluation of people older than 65 years, the number of patients with KOA was 6 million, in which 3.8 million were women and 2.2 million were men, respectively [24].

ETIOLOGY

KOA is known as the series of progressive articular disorders that the exact cause of its occurrence is unknown. However, any factor which can disrupt the physiological balance between anabolic and catabolic activity of the chondrocytes can be identified as the etiology of KOA. KOA has been attributed to the involvement of several etiological factors, these factors are mainly classified into systemic and local factors [8, 25].

Metabolic or endocrine diseases can also increase the risk of KOA. Some of these diseases which can promote KOA are as follows: rickets, acromegaly, hyperparathyroidism, diabetes and gout. Moreover, any other disease that leads to bone marrow edema, inflammation of synovial tissue and disorders such as chondrocalcinosis can increase the risk of KOA, dramatically [26, 27].

Furthermore, some exogenous risk factors such as obesity, trauma and sedentary lifestyle can activate different pathological pathways in KOA. For instance, in traumatic patients, increasing serum level of cytokines and chemokines as well as activation of the NF- κ B pathway have been observed [28, 29].

PATHOPHYSIOLOGY

The emergence of KOA is the result of an imbalance in anabolic and catabolic pathways in chondrocytes [30]. Disruption of this balance causes some irreversible changes in the knee joint. The first events which happen in KOA are the dysfunction of the chondrocytes and matrix degradation [31]. However, this is not the only pathological change caused by KOA. The entire joint structure such as subchondral bones, meniscus, ligaments, synovial membrane, joint capsule and periarticular muscles can be affected as well [32]. Significant structural changes in KOA have been illustrated schematically in Figure.

One of the most important symptoms of KOA is the presence of osteophytes. After the degradation of articular cartilage as an initial sign of KOA, bone remodeling occurs in response to this destruction. Therefore, abnormal bone remodeling process in the subchondral bones leads to osteophytes formation [33]. Subchondral bone sclerosis and subchondral bone cysts are other symptoms of KOA which can be seen in the latest stages of the disease. By the progression of the disease, some angiogenic factors are generated because of progression in the bone remodeling process. Increased blood flow to the subchondral bones can lead to bone sclerosis and cyst formation in these areas [34]. Furthermore, inflammation of the synovial membrane, synovitis, is another pathological symptom of KOA. Synovitis can lead to severe knee swelling which is accompanied by pain [35].

DIAGNOSIS

The diagnosis is mainly made by physical examination, imaging and laboratory tests. While, under certain circumstances, nuclear medicine-based techniques such as scintigraphy may also be recommended for better diagnosis.

Physical examination

In the first stage, it is important to obtain a history of the disease and its related events, as well as to ask about the history of other diseases in the patients. Then, evaluation of the symptoms which mentioned above by physicians and sometimes by the use of some questionnaires such as Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Visual Analogue Scale

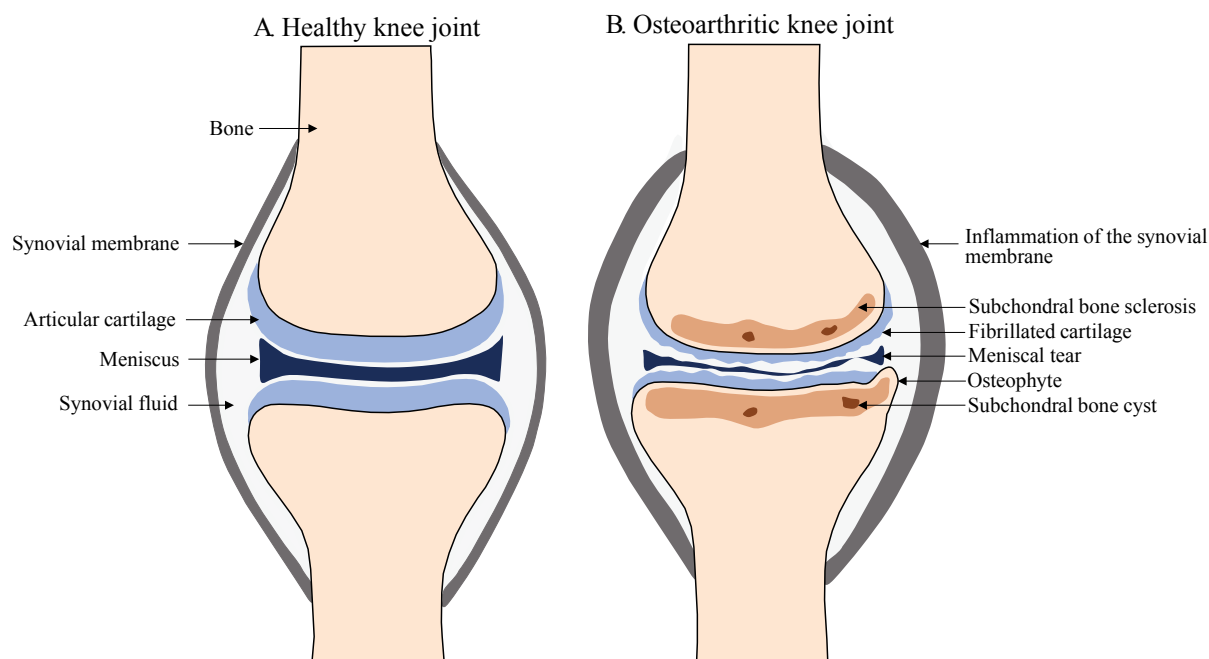


FIG. Structural comparison of osteoarthritic knee with healthy knee. A: healthy knee joint with soft bone surface, normal meniscus and articular cartilage. B: in osteoarthritic knee, osteophytes, bone cysts and sclerosis occurred in subchondral bones. Fibrillated cartilage, meniscal tear, and inflammation of synovial membrane are other abnormalities could be seen in osteoarthritic knee joint.

РИС. Сравнение структуры здорового коленного сустава и при остеоартрите. А: здоровый коленный сустав с мягкой костной поверхностью, нормальным мениском и суставным хрящом. В: при остеоартрите коленного сустава в субхондральной кости формируются остеофиты, костные кисты и склероз. Другие изменения, которые можно увидеть при остеоартрите коленного сустава: фибриллированный хрящ, разрыв мениска и воспаление синовиальной оболочки.

(VAS) and Knee Injury and Osteoarthritis Outcome Score (KOOS) leads to diagnosis of KOA [36–38]. In addition to examining these symptoms, a full physical examination should be performed by the orthopedic physician.

Although physical examination is necessary for the diagnosis of KOA, it is not sufficient to evaluate and determine the progression of the disease. Other diagnosis methods are usually used in cooperation with physical examination to more accurately diagnose and determine the grade of disease that is required to choose an effective treatment.

Imaging-based diagnosis

Imaging-based methods have been known as one of the common methods which are used to accurately diagnose KOA by evaluating the morphological changes that have occurred. Depending on the patient's condition, one or more of these methods are required by the orthopedic physician.

Radiography is the most appropriate diagnostic method among various imaging techniques. KOA is diagnosed with morphological changes such as osteophytosis, appearance of cysts, joint space loss or narrowing, subchondral sclerosis and abnormalities in the bone such as rounded femoral condyle. Then, by observing one or more of these features in the radiography analysis, the progression degree of KOA is diagnosed.

The Kellgren-Lawrence classification is the most important classification to determine the progression extent of KOA divided into five grades which have been determined as follows: grade 0: absolute absence of radiographic features; grade 1: beginning of osteophyte formation and doubtful joint space narrowing; grade 2: definite osteophytosis and possibility to observe joint space narrowing; grade 3: multifarious osteophytes, sclerosis, joint space narrowing and probability of bone deformation; grade 4: giant osteophyte, intensive sclerosis and joint space narrowing, bone deformation, notably in the head of femur [39]. Although radiography provides an objective measurement of KOA, it does not give a complete view of the soft tissue. For instance, degenerative changes of ligaments, meniscus and cartilage, whose early diagnosis can lead to the prevention of KOA, cannot be detected by radiography.

MRI has received much attention in the diagnosis of KOA, especially early KOA, damage to soft tissue structures such as ligaments injuries, meniscuses rupture, synovitis changes, bone marrow lesions and effusions can be diagnosed by MRI. Furthermore, the importance of MRI is in the ability to diagnose early KOA [13].

More imaging-based methods include computed tomography scan, sonography, arthroscopy and scintigraphy, which are less commonly used for the diagnosis of KOA.

Laboratory tests

Laboratory tests can be used as another method for diagnosis of KOA. The use of this diagnostic method is not as common as the methods which are suggested in the previous sections, but it may be useful for a more accurate diagnosis depending on the patient's condition. Laboratory tests on blood, urine and synovial fluid are usually performed to assess the presence or absence of inflammatory diseases that may lead to symptoms such as the symptoms of KOA. In suspected cases of inflammatory diseases such as gout and rheumatoid arthritis, the use of laboratory tests can help diagnose KOA and exclude the inflammatory diseases or confirm the presence of them [40].

Measurement of biomarkers

One of the novel diagnostic methods for KOA as an inflammatory disease, is the measurement of specific biochemical markers in blood, plasma, urine, and synovial fluid samples. Evaluation of these biomarkers provides useful clinical information. In 2006, Bauer and colleagues proposed the BIPED classification for KOA biomarkers. This classification is based on the effectiveness of biomarkers in the Burden of disease, investigative, prognostic, Efficacy of intervention, and Diagnostic [41]. Ten years later, Kraus et al. evaluated 18 biomarkers as predictors of KOA. They measured these markers in 194 patients with KOA over 12 and 24 months. The results of this study showed the compatibility of the level of these markers with radiographic images of patients and the severity of the disease during this period [42].

Assessment of KOA biomarkers in the blood were considered more than synovial fluid and urine due to availability. In this regard, cartilage oligomeric matrix protein and hyaluronic acid (HA) in blood are among biomarkers that are very common for diagnosing KOA. Cartilage oligomeric matrix protein is a component of cartilage tissue and synovial fluid. Since this protein is present only in this organ, its measurement in the blood can indicate the destruction or repair of the cartilage tissue [43]. HA as another marker, is one of the heavy molecules of glucosamine, which is a component of connective tissue.

Studies have shown that the presence of HA in the blood is associated with synovial fluid volume [44]. Furthermore, other biomarkers exist in this field and examining several biomarkers can lead to a more accurate diagnosis of KOA. For instance, matrix metalloproteinase (MMP)-1, MMP-3 and MMP-13 can be considered as diagnostic markers that their levels in blood are directly related to reduction of cartilage volume [45]. C-terminal crosslinking telopeptide of type II (CTX-II) is another momentous biomarker that its level in blood and urine indicates the amount of destruction in the cartilage [46]. Moreover, examining the level of some cytokines such as interleukin (IL)-1, IL-6, IL-10, IL-8, IL-11 and tumor necrosis factor (TNF)- α can be useful in evaluation of the

progression of the disease or its improvement [47, 48]. Evaluation of these biomarkers is mainly done by the use of Enzyme-Linked Immunosorbent Assay (ELISA) [49].

Local (in synovial fluid) and systemic (in blood) evaluation of the biomarkers which mentioned above, can be useful in the early diagnosis of the disease. Evaluation of these inflammatory markers besides the available disease evidence such as joint space narrowing and the volume of cartilage which are obtained by imaging-based methods, lead to early diagnosis of the KOA. Furthermore, by the use of these data, the extent of progression or improvement of the disease under various treatments can be achieved.

TREATMENT

Different techniques have been published for KOA treatment that some of them are known as the standard treatment, and others are still in the investigation [50]. Choosing treatment methods are depending on several parameters, which are pain and knee function, KOA stage, and patient-related factors such as age, level of physical activity, and patient's comorbidities [51]. Conventional treatments are divided into two main classes, surgical and non-surgical. While, in the last decade, several innovative methods such as cell therapy related to tissue engineering and regenerative medicine have been considered.

Non-surgical treatments

Non-surgical treatments are the primary methods used for the treatment of this degenerative disease [52]. Because of their ease, safety, and cost-effectiveness, they are known as pain relief treatments. In this regard, Osteoarthritis Research Society International (OARSI) released an updated guideline in which they recommended arthritis education and exercise for patients with KOA as a core treatment [53]. Moreover, ACR proposed non-steroidal anti-inflammatory drugs (NSAID) and intra-articular glucocorticoid injections as the first line treatment for KOA in addition to recommendation for exercise and weight loss [15]. Generally, non-surgical treatments are divided into two groups, which are pharmacological and non-pharmacological treatments.

Non-pharmacological treatments

Non-pharmacological treatments are the first line therapeutic strategy for majority of the patients. As already mentioned, obesity is one of the main etiologies for initiation and development of KOA; hence weight management and proper physical exercise are known as non-pharmacological approaches in OA [54]. Walking canes and biomechanical interventions like braces are the other primary non-pharmacological methods for KOA. In this regard, studies showed that usage of knee braces and foot orthoses could positively relieve pain and stiffness of the knee [55]. Although walking canes are appropriate for KOA, they are not appropriate for multi-joint OA because they may increase weight loading on other affected joints [56].

Pharmacological treatments

Pharmacological treatments are the second group of non-surgical treatments. Different medicinal components have been investigated to relieve the pain and reduce the KOA complications. These drugs are mostly used in the mild to moderate stages [57]. NSAIDs are the common drugs which are used as first-line KOA treatment. Studies showed that NSAIDs can control the pain better and have lower risks, compare to other drugs. However, it has led to the appearance of the cardiovascular disorders among patients who used selective NSAIDs. Hypertension, congestive heart failure, and renal toxicity are known side effects of NSAIDs. Intra-articular steroid administration is the other pharmacological treatment for KOA. In 1960, Wright *et al.* showed an effective pain relief after steroid injection. However, there were some reports of cartilage damage and infectious arthritis, that causing limitation of this drug [58].

HA injection, is widely used as a pain relief therapy to improve joint function [59]. HA as an important component of articular cartilage has different functions in the knee, which includes synovial joints lubrication, shock absorption, and structure stabilization and also has direct effects on the function of synovial cells. However, some allergic side effects have been seen in HA injection related to the origin of this product (animal derived glycosaminoglycan, such as cockscomb tissue). Pain and swelling after injection could be related to the high molecular weight and different pharmaceutical formulations of HA [60]. The other major challenge of treatment with HA is the multiple injection requirement in order to get to the desired efficiency. Multiple injections itself could have more cost, pain, and possibility of infection [61].

Glucosamine is known as one of the popular pharmacological treatments in KOA [62]. Remarkable pain relief in the patients in mild to moderate stages with lower side effects is the advantage of this therapy. It is commonly used as an alternative treatment, especially for mild to moderate KOA. However, it cannot be determined as a treatment since there was not any difference between glucosamine and placebo in recent studies [63].

Surgical treatments

If non-surgical techniques fail to improve the condition, surgical techniques could be prescribed. Standard surgical treatments for KOA include arthroscopy, osteotomy, knee arthroplasty [64]. Although mosaicplasty, a technique for cartilage repair using osteochondral autograft transplantation, is known as another surgical option [65]. The choice of appropriate procedure depends on several factors, including the stage of KOA, age of the patients and comorbidities.

Arthroscopy includes two separate techniques, lavage and debridement of the knee [66]. Evidence shows that there is not any significant difference between these two techniques and placebo surgery for patients with KOA. Although arthroscopy as a minimally invasive and low-cost surgery is preferable by patients, these patients

could not benefit from arthroscopy due to its short-lived effectiveness [5]. Although arthroscopic lavage and debridement could be a useful treatment approach for the patients with symptomatic meniscal damage with locking symptoms [67, 68].

In the advanced stage of KOA, Joint arthroplasty is a well-accepted, safe and cost-effective method. This approach is mostly used for the patients who did not respond to other treatments. Nevertheless, this technique is limited in the durability of prosthetic components, which is about 15–20 years [69]. Uni-compartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA) are two different types of arthroplasty. The grade of KOA and involved compartment of the joints are two key factors to determine suitable arthroplasty technique. UKA recommended more than TKA because of shorter recovery period, better performance, and better subjective feeling due to the natural knee tissue which is used. However, UKA is usually proposed only for the patients whose medial compartment is involved with KOA, and TKA suggested for patients with lateral compartmental KOA [70].

Osteotomy is another surgical technique mostly used for the patients with uni-compartmental KOA in early stages. In knee osteotomy, the tibia or femur is cut and then reshaped to relieve the pressure on the damaged knee joint. This technique was widely used for a long time; however, due to its complications such as failure to healing and stiffness of the knee after surgery, has been replaced with arthroplasty [71]. Recent development of new locking plates and the tendency to open-wedge osteotomy without bone graft led to a revival of osteotomy for younger patients [72].

There are some techniques that can help cartilage repair. One of these techniques is the autologous osteochondral transplantation (mosaicplasty). In this technique, one or several cylindrical plugs which have been taken from the peripheries of the femoral condyles transfer to the defect sites. This procedure can be open (for large defects) or arthroscopic (for small defects) [65]. Minor integration, limited graft availability, and technical difficulties are the disadvantages of this procedure [73].

Tissue engineering

Needs for a method to repair the cartilage with less cost and high efficiency led to the entrance of tissue engineering and regenerative medicine in KOA treatment. The purpose of KOA treatment is to reduce or eliminate pain, correct deformity, improve or restore joint function, and improve quality of life. Various regenerative medicine approaches including mesenchymal stromal cells (MSCs), platelet-rich plasma (PRP), and amniotic fluid in combination with cartilage tissue engineering methods could present novel techniques to repair the Cartilage tissue [74].

Recently, cartilage tissue engineering developed as a result of progress in biomaterial science. In tissue engineering cells are seeded onto a scaffold which

mimicking the extracellular matrix (ECM). Polymeric scaffolds in different forms were the first group of scaffolds used for cell culture in tissue engineering [75]. Vacanti et al. in an animal study showed that synthetic polymer of polyglycolic acid (PGA) could be a useful scaffold in the cartilage tissue engineering [76]. In 2006 Wang et al. combined adult human chondrocytes (hCHs) with aqueous-derived porous silk fibroin scaffolds for *in vitro* cartilage tissue engineering. They compared their results with a previous study in which they used MSC. Both studies showed that silk fibroin scaffold would be a good choice in cartilage tissue engineering [77]. In 2017, they also proposed nanohydroxyapatite-chitosan-gelatin micro-scaffolds (HaCGMs) as a new injectable scaffold for cartilage repair in subchondral bone lesion rabbit model. The results showed suitable swelling ratios, bioactivity, porosity, stiffness and also showed high cellular infiltration [78]. Choosing the appropriate cell source is another important issue of tissue engineering and regenerative medicine. The cell sources usually used for cartilage tissue engineering are chondrocytes, fibroblasts, and MSCs. Recently, MSCs absorb the researcher's attention in order to use them as a suitable cell source in the cartilage tissue engineering [79].

Mesenchymal stromal cells

The use of chondrocytes in applications of cartilage tissue engineering has some limitations, in donor-site morbidity, cell de-differentiation, and the limited lifespan [80]. It has been shown that MSCs do not produce these concerns. Due to regenerative and immunomodulatory characteristics of MSCs, they have become an alternative cell source in cartilage tissue engineering in the last decade [81]. Friedenstein et al. and Chamberlain et al. were the first researchers that used MSCs to treat OA [82, 83]. Pittenger et al. demonstrated that the MSCs could be cultured and amplified without loss of multipotent differentiation potential [84]. MSCs could be found in several tissues such as bone marrow, periosteum, trabecular bone, fat pad tissue, synovial membrane, skeletal muscle, and deciduous teeth. Moreover, they could differentiate into the variety of cell lineages such as osteoblasts, adipocytes, chondrocytes, and myocytes [79].

Another requirement for cartilage regeneration in order to achieving high therapeutic effect is implantation methods. In this way, tissue engineering helps to develop scaffolds as a carrier and nutrient supply for the stem cells in the microenvironment [85]. The common biomaterials that have been used for MSCs implants are Collagen, HA, electrospun fibers and recently novel tissue engineering approaches such as Agili-C, Hyalograft C, and Chondrotissue [86]. In the first line, safety and efficacy of any procedure have been analyzed *in vitro*. In this regard, the osteogenic differentiation of BM-MSCs associated with an aragonite-based scaffold (Agili-C™, CartiHeal Ltd.) was evaluated. The results of their study showed that this method could be effective in regeneration of osteochondral defects [87]. In the next step and

in an animal model investigation, Kayakabe et al. used HA gel sponge as a carrier to transplant the autologous bone marrow stem cells to the rabbit joint model. The result demonstrated that it can effectively repair damaged articular cartilage. After 12 weeks, cartilage repair was observed, which means that the HA gel sponge can positively affect cartilage regeneration [88]. Moreover, the efficacy of AD-MSCs and carboxymethyl chitosan on OA in rabbit model was investigated in 2020. Total number of thirty New Zealand rabbits in five different groups underwent intra-articular injection after making defects in their joints. The results of this study demonstrated that injection of AD-MSCs and carboxymethyl chitosan leads to cartilage repair [89]. In the other pre-clinical study, Guo et al. have utilized autologous MSCs bio-ceramic β -triphosphate scaffold to treat OA in sheep model [90]. The other animal study, which was done in 2017, introduced 3D-printed poly(ϵ -caprolactone) scaffold in combination with MSCs as a functional product for articular cartilage regeneration in rabbit model [91]. Investigation about cartilage tissue engineering and MSCs therapy has been continued with clinical trials. In this regard, the efficacy of filtered bone marrow aspirate containing MSCs in combination with biomimetic collagen-hydroxyapatite scaffold in KOA was investigated on 15 patients. This research showed significant improvement in the status of the patients [92]. PRP is one of the cartilage growth factors which is rich in TGF- β , Koh et al. reported that the injection of MSCs in combination with PRP into the joint cavity showed significant improvement in the treatment of OA [93]. Besides the usage of carriers, MSCs has been injected locally which has many advantages not only enhance joint repair, but also reduce OA-induced degeneration which is the simplest method for treating OA [94].

Although scaffolds, especially biological ones, have a good impact on cartilage repair, injection of cells without scaffold is currently used in most clinical trials. This technique not only accelerates the cartilage repairs but also reduces the need for surgery and pain of scaffold implantation [95]. Impressive *in vitro* and *in vivo* results in cartilage repair using MSCs have led to the development of various clinical trial studies using MSC for the treatment of KOA. Akgun et al. were one of those who conducted a single center, randomized, and controlled trial. They demonstrated that MSCs can effectively accelerate the repair of cartilage defects [96]. Numerous clinical trials [97–105] have been performed in this field that some of them mentioned in Table.

Clinical trials using MSCs injection for the treatment of KOA have demonstrated this treatment as a successive approach. However, it has some issues that should be considered. Autologous or allogeneic cell source is still a challenge that several studies have been working on. Besides the cell source, cell contamination is the other criterion that should be paid attention to in each study [106].

Table. Clinical studies of knee osteoarthritis treatment with intra-articular injection of mesenchymal stem cells

Таблица. Клинические исследования применения внутрисуставных инъекций мезенхимальных стволовых клеток в лечении остеоартрита коленного сустава

Type of study / Тип исследования	Methods / Лечение	Measurement / Методы оценки эффективности	Result / Результат	Author [ref] / Автор [источник]
Non-blinded RCT / Открытое РКИ	Autologous BM-MSCs (1.46 ± 0.29) $\times 10^7$ in conjunction with microfracture and medial opening-wedge high tibial osteotomy / Аутологичные МСК КМ (1.46 ± 0.29) $\times 10^7$ в сочетании с высокой тиббиальной остеотомией	IKDC, Lysholm and Tegner scores, MRI / Шкалы IKDC, Лисхольма и Тегнера, МРТ	Improvement for all scores. MRI after 1 y showed significantly better MOCART scores for the cell-recipient group / Улучшение показателей по всем шкалам. В группе МСК КМ получены значимо лучшие результаты МРТ через год по шкале MOCART	Wong K.L. et al. [97]
Triple-blind placebo-controlled RCT / Тройное слепое плацебо-контролируемое РКИ	Autologous BM-MSCs 40×10^6 / Аутологичные МСК КМ 40×10^6	WOMAC, VAS / WOMAC, ВАШ	The BM-MSCs treated group had significant clinical improvement as compared to the placebo group in all clinical endpoints / По всем клиническим конечным точкам более значимый эффект в группе МСК КМ по сравнению с группой плацебо	Emadedin M. et al. [98]
Double-blind RCT / Двойное слепое РКИ	Three groups: allogeneic MSCs 50×10^6 (group A) and 150×10^6 (group B) and a sodium hyaluronate (control group) following partial medial meniscectomy / Аллогенные МСК 50×10^6 (группа А) и 150×10^6 (группа В) после частичной медиальной менискэктомии	MRI, self-explanatory questionnaires / MPT, опросники	Increased meniscal volume determined by quantitative MRI in 24% of patients in group A and 6% in group one-year post meniscectomy. Patients in groups A and B experienced a significant reduction in pain compared to control group / Увеличение объема мениска спустя год по данным МРТ у 24% пациентов в группе А и у 6% в группе В. В группах А и В отмечено значительное уменьшение боли по сравнению с группой контроля	Vangsness Jr C.T. et al. [99]
Phase I/II study / Исследование I/II фазы	Autologous MSCs $40.9 \times 10^6 \pm 0.4 \times 10^6$ / Аутологичные МСК $40,9 \times 10^6 \pm 0,4 \times 10^6$	Walking time, VAS and MRI / Время ходьбы, МРТ, ВАШ, рентген	Decrease in the intensity of pain since day 8 after the infusion, that was maintained after 12 mo. T2 mapping showed signs of cartilage regeneration in all patients at 12 mo post-treatment / Снижение интенсивности боли с 8 дня, сохранение эффекта через 12 мес. Признаки регенерации хряща у всех пациентов по T2-картированию через 12 мес.	Soler R. et al. [100]
Double-blind placebo-controlled RCT, phase II study / Двойное слепое плацебо-контролируемое РКИ, фаза II	Allogeneic MSCs in four different doses: 25, 50, 75, and 150×10^6 / Аллогенные МСК в четырех различных дозах: 25 \times , 50 \times , 75 \times и 150×10^6	VAS, ICOAP and WOMAC / ВАШ, ICOAP и WOMAC	A 25×10^6 cell dose may be the most effective among the doses; WOMAC, ICOAP, and VAS scores decreased by the time of the final follow-up period / Доза 25×10^6 оказалась самой эффективной. Показатели по шкалам WOMAC, ICOAP и ВАШ снизились к периоду завершения наблюдения	Gupta P.K. et al. [101]
Phase I/II study / Исследование I/II фазы	Autologous MSCs 30.5×10^6 / Аутологичные МСК $30,5 \times 10^6$	MRI and KOOS / MPT и KOOS	Significant improvement in the KOOS and knee cartilage thickness / Значительное улучшение KOOS и толщины суставного хряща коленного сустава	Al-Najar M. et al. [102]
Phase I/II study / Исследование I/II фазы	Stimulated autologous BM-MSCs / Стимулированные аутологичные МСК КМ	VAS, WOMAC / ВАШ, WOMAC	Significantly reductions in pain and increased quality of life after 6 mo / Значительное уменьшение боли и улучшение качества жизни через 6 мес.	Garay-Mendoza D. et al. [103]
Double-blind RCT, phase I/II / Двойное слепое РКИ, фаза II	Three groups: hyaluronic acid at baseline and after 6 mo, single-dose (20×10^6) at baseline, and repeated UC-MSCs doses at baseline and 6 mo (20×10^6) / Три группы: гиалуроновая кислота исходно и через 6 мес. МСК из пуповины (20×10^6) однократно и двукратно: исходно и через 6 мес.	WOMAC, MRI / WOMAC, МРТ	UC-MSCs treatment is safe and superior to active comparator at 1-year follow-up / Лечение МСК из пуповины безопасно и превосходит препарат сравнения при наблюдении в течение 1 года	Matas J. et al. [104]

Type of study / Тип исследования	Methods / Лечение	Measurement / Методы оценки эффективности	Result / Результат	Author [ref] / Автор [источник]
Single-blind placebo-controlled RCT / Простое слепое плацебо-контролируемое РКИ	Three groups: AD-MSCs (10×10 ⁶), AD-MSCs (10×10 ⁶) and LIPUS, normal saline injection and LIPUS / Три группы: МСК ЖТ (10×10 ⁶), МСК ЖТ (10×10 ⁶) и LIPUS, инъекция изотонического раствора и LIPUS	WOMAC, MRI, VAS / WOMAC, MPT, ВАШ	Combination of AD-MSCs and LIPUS could be more effective in pain relief / Сочетание МСК ЖТ и LIPUS более эффективно в уменьшении боли	Nasb M. et al. [105]
Non-blinded RCT / Открытое РКИ	Three groups: autologous AD-MSCs (100×10 ⁶) single and double dose (at baseline and 6 mo), control group / Три группы: МСК ЖТ (100×10 ⁶) однократно и двукратно (исходно и через 6 мес.), контрольная группа	KOOS, WOMAC, MRI / KOOS, WOMAC, MPT	AD-MSCs (single and double dose) therapy appears to be a safe and effective / МСК ЖТ (однократное и двукратное введение) безопасна и эффективна	Freitag J. et al. [18]

Note: AD-MSCs, BM-MSCs, UC-MSCs – adipose, bone marrow, umbilical cord derived mesenchymal stem cells; RCT – randomized controlled trial; MRI – magnetic resonance imaging; ICOAP – intermittent and constant osteoarthritis pain; IKDC – International Knee Documentation Committee; KOOS – knee injury and osteoarthritis outcome score; LIPUS – low-intensity pulsed ultrasound; MOCART – magnetic resonance observation of cartilage repair tissue; VAS – visual analogue scale; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index

Примечание: МСК ЖТ, МСК КМ – мезенхимальные стволовые клетки жировой ткани, костного мозга; РКИ – рандомизированное контролируемое исследование; MPT – магнитно-резонансная томография; ВАШ – визуально-аналоговая шкала; ICOAP – перемежающаяся и постоянная боль при остеоартрите; IKDC – Международный комитет по документации обследования коленного сустава; KOOS – оценка исхода травмы и остеоартроза коленного сустава; LIPUS – импульсный ультразвук низкой интенсивности; MOCART – магнитно-резонансная оценка восстановления хрящевой ткани; WOMAC – индекс выраженности остеоартрита Университетов Западного Онтарио и МакМастера.

CONCLUSION

KOA is counted as a second disease among individuals. Hence investigations to find appropriate methods for diagnosis and treatment are always in the interest of researchers. By the advance of biomaterial and tissue engineering, a new sight has been opened in this area. Biomarkers and MSCs are the most effective factors in the development of new methods for KOA diagnosis and treatment.

Diagnosis of KOA in the early stages can lead to more effective and less costly treatment for the disease. Despite the existence of many common diagnostic methods, the diagnosis of KOA in the early

stages cannot be made most of the time. Detection of the relationship between some biomarkers level in the blood, urine, or synovial fluid and OA progress helped doctors on the diagnosis of this disease in its early stage.

Cartilage repair with different kinds of scaffolds showed promising outcomes that indicate tissue engineering could help KOA treatment. However, the use of MSCs without scaffold would be more effective due to the reduction of surgery and extra pain for the patients. Even though different clinical trials have been done, more investigations need for achieving a safe and highly effective treatment approach.

AUTHOR CONTRIBUTIONS

Bahareh Sadri and Shirin Nouraein searched and analyzed the literature on the review topic. Bahareh Sadri and Nikoo Hosseini-Khannazer participated in writing the text of the manuscript and its interpretation. Massoud Vosough and Javad Mohammadi developed the general concept of the article and supervised its writing. All authors participated in the discussion and editing of the work. All authors approved the final version of the publication.

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Б. Садри и Ш. Нуран провели поиск и анализ литературы по теме обзора. Б. Садри и Н. Хоссейн-Ханназер участвовали в написании текста рукописи и интерпретации данных. М. Восо и Д. Мохаммади разработали общую концепцию статьи и руководили ее написанием. Все авторы участвовали в обсуждении и редактировании работы. Все авторы одобрили окончательную версию публикации.

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