Tissue and Cell 80 (2023) 101992

Contents lists available at ScienceDirect

Tissue and Cell

journal homepage: www.elsevier.com/locate/tice

Review

Challenges in osteoarthritis treatment

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ARTICLE INFO

Keywords:
Osteoarthritis
Cartilage tissue engineering
Exosomes
Cartilage gene therapy
Surgical techniques
Joint anatomy

ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis and a degenerative joint cartilage disease that is the most common cause of disability in the world among the elderly. It leads to social, psychological, and economic costs with financial consequences. The principles of OA treatment are to reduce pain and stiffness as well as maintain function. In recent years, due to a better understanding of the underlying pathophysiology of OA, a number of potential therapeutic advances have been made, which include tissue engineering, immune system manipulation, surgical technique, pharmacological, and non-pharmacological treatments. Despite this, there is still no certain cure for OA, and different OA treatments are usually considered in relation to the stage of the disease. The purpose of the present review is to summarize and discuss the latest results of new treatments for OA and potential targets for future research.

1. Background

One of the most common joint disorders is AO (Hawker, 2019). People over the age of 60 suffer from joint inflammation to some extent. Osteochondritis occurs in many joints and can involve all joints (Takeda et al., 2021). Normal articular cartilage of hyaline is needed for usual knee motion (Suh et al., 2021) For this feature in the natural joint articular cartilage and subchondral bone form the load-bearing system that provides a large range of joint motion with excellent lubrication, stability, and uniform distribution of high-acting loads. Articular cartilage (AC) together with subchondral bone plays a very important role in the natural joints (Lin and Klein, 2021). Cartilage protects the subchondral bone from high stresses and increases joint congruence thereby reducing nominal contact pressure and allowing for low-friction movements within the joint (Bowland et al., 2018).

Due to the blood supply to the articular cartilage, the access to the source of progenitor cells and the mitotic activity of the chondrocytes is low, therefore, large cartilage lesions regenerate spontaneously and may cause the progression of cartilage destruction and eventually OA (Verhagen et al., 2003). Previous study has reported that various factors such as the size and side of the lesion or the type of loading can be effective in tissue repair. Also, age is one of the factors that play a role in cartilage repair. Due to the increase in traumatic injuries and arthritis and on the other hand, the lack of proper treatment for them, joint osteochondral reconstruction remains a clinical challenge (Wei and Dai, 2021). Therefore, the purpose of this paper is to review and suggest the available treatment for OA.

2. Anatomy of Natural joint

The natural joint has two parts: articular cartilage and subchondral bone. Articular cartilage is formed by 2 phases; the solid phase and a fluid phase include about 15–32% and 68–85% of the total, respectively (Wei and Dai, 2021). Collagen and proteoglycans form the solid phase and the fluid phase is mainly composed of water. Articular cartilage makes a flat surface with the lowest friction that transfers body weight from the joint to the underlying subchondral bone. Cartilage has the ability to transmit high powers although low hardness and this feature is due to the leakage and movement of fluid within the spongy part of cartilage. Furthermore, synovial fluid besides articular cartilage creates a friction factor near 0.008 (Şenol and Özer, 2020). Subchondral bone is slim, firm, and layered and links the articular cartilage and the compact bone together. It is composed of a rich extracellular matrix such as collagen fibers, calcium, and phosphate. The subchondral bone plays an important role in the transfer of load from articular cartilage to compact bone. Subchondral bone has the capability to change its structure according to the shape of the joint. The orientation of collagen fibrils in subchondral bone causes functional adaptation in the microenvironment (Lin et al., 2020).

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https://doi.org/10.1016/j.tice.2022.101992
Received 22 September 2022; Received in revised form 16 November 2022; Accepted 25 November 2022
Available online 28 November 2022
0040-8166/

2.1. Osteochondral defects

The origin of the cartilage and subchondral bone degradation is still unknown but generally, these injuries occur frequently as a result of trauma, tumor, or OA. One of the theories is that the subchondral bone becomes weaker, loose, and cannot capable to transfer the power to the cancellous and cortical bones. Subsequently, the cartilage will be fractured and fragile (Alousaimi, 2018).

In joints, the surface cartilage is spoiled and causes pain, reduction of motion, and joint rigidity (Zampogna et al., 2020). First-person that describe the term "osteoarthritis" was Monro and König (Schuman et al., 2002). They suggested that this problem was the result of necrosis, spontaneously. After that, other factors have been described including traumatic, embolic, hereditary, endocrine, developmental, and idiopathic (Verhagen et al., 2003).

Due to the blood supply of articular cartilage, accessibility to the source of progenitor cells and mitotic activity of chondrocytes is low, so, large cartilage lesions spontaneously regeneration mostly fail and may cause progression of cartilage destruction and finally OA (Verhagen et al., 2003). Previous studies have reported that different factors including the size and side of the lesion, or the type of loading, affect tissue repair. Also, age is one of the factors involved in cartilage repair. Previous studies have shown that defects that cause perforation in the subchondral bone are ably repaired in young animals, whereas in older animals, in both partial (destruction of cartilage alone) or full thickness (simultaneous damage to cartilage and subchondral bone) are unable to successful repairing (Wei and Dai, 2021).

The challenges for osteoarthritis treatment are difficult because of two reasons: The first pathogenesis of OA is a combination of mechanical pathology and biological response to mechanical damage, both of them seem to be additive in causing joint damage and pain (Felson and Neogi, 2018). If one of the factors is not considered, the treatment may fail in some people. Second, the relationship between pain relief and improving the structure is not linear. In some cases, pain relief may lead to structural deterioration and create an additional challenge to treatments that aim to improve both (Felson and Neogi, 2018). In the following, however, we suggest treatments that may be insufficient.

2.2. Tissue engineering for OA and cartilage defect

The tissue engineering approach can be a good alternative to cartilage regeneration. In cartilage tissue engineering, scaffold, cell, microenvironment, mechanical stimuli, and biomaterial interaction with cells are among the parameters affecting cartilage repair. The designed scaffold must be able to mimic the mechanical properties of native tissue, as well as support long-term cartilage function.

2.3. Scaffold

Preparing a suitable substrate for the three-dimensional growth of cells plays an essential role in the success of tissue engineering implants (Banani et al., 2021). Scaffolds are of natural or artificial origin. Decellularized natural tissues are among natural substrates. Decellularization of natural tissues due to having the correct macromolecular structure can provide a suitable platform for cartilage tissue engineering (Lammi et al., 2018). In the decellularization process, to eliminate any possible transmission of disease, all factors that increase immune responses and the risk of rejection of implanted materials such as cellular materials must be reduced. Meanwhile, the tissue structure and mechanical properties should be maintained. Cartilage and meniscal tissue have a large ECM and obtaining correct cell colonization and penetration of cells deep into the decellularized substrate are among the challenges (Lammi et al., 2018).

Based on previous research, various materials have been used to prepare articular cartilage for OA regeneration, and some of them have been able to mimic the complexity of cartilage ECM. Artificial scaffolds are prepared by various techniques such as electrospinning, solvent casting, particle leaching, gas foaming, and freeze drying, as well as stereolithography, and 3D bioprinting to produce scaffolds in cartilage tissue engineering (Vyas et al., 2017).

Based on previous research, various materials have been used to prepare articular cartilage to regenerate OA, and some of them have been able to mimic the complexity of the cartilage ECM network (Makris et al., 2015; Reddi et al., 2011). Biomaterials Scaffolds are synthesized from both natural and artificial sources. Among the benefits of natural resource-derived biopolymers that are widely used for cartilage tissue engineering is support for cell binding, viability, proliferation and differentiation, and preservation of cell phenotype (Tchobanian et al., 2019). Natural polymers fall into two categories: polysaccharide-based polymeric materials such as alginic acid, cellulose, and chitin, and protein-based polymeric materials such as collagen, gelatin, and silk fibroin (Tchobanian et al., 2019). Limited processability and poor mechanical properties are the challenges of using natural materials in osteochondral tissue engineering. However, the properties of natural materials can be improved through cross-linking mechanisms or by a combination of other factors (Tchobanian et al., 2019). For example, the mechanical and physical properties of collagen can be improved by cross-linking with glutaraldehyde (Arabpour et al., 2019; Simorgh et al., 2021). The mechanical and physical properties of gelatin another widely used natural biomaterial in cartilage regeneration are modified by a reaction with methacrylic anhydride and the formation of gelatin methacrylate (GelMA). In addition, gelatin methacrylate is sensitive to UV light and changes state at certain wavelengths, and can be a good choice for bio-ink in a 3D bioprinting system (Yue et al., 2015). Hydrogels are a group of materials that can act as promising scaffolds for cartilage regeneration due to their viscoelastic properties, high water content, and formability match to the defect. Hydrogels designed in tissue engineering should be non-toxic, biocompatible, and biodegradable, and in addition, should not stimulate the immune system and cause inflammation (Eslahi et al., 2016).

Synthetic polymers have better physical and mechanical properties than natural polymers. In addition, due to the ability of chemical modification, the properties of materials can be adjusted according to the native tissue (Rodríguez-Vázquez et al., 2015). Synthetic polymers are less prone to cellular binding than natural polymers. Of course, there are various ways to overcome these challenges, including creating an agent for the polymer with cell adhesive markers and also combining it with bioactive polymers (Skaalure et al., 2014). In previous research, polycaprolactone (PCL) polymer has been widely used in cartilage tissue engineering due to its favorable mechanical properties. This polymer in the molten state has a suitable elastic for extrusion through melt extrusion and melt electrospinning for cartilage tissue engineering (Mekhileri et al., 2018). Polyethylene glycol (PEG) is another polymer that has received much attention in recent years due to the formation of covalently compatible networks between the cell and the polymer as an active reaction agent to regulate cell binding on the surface of the polymer (Mekhileri et al., 2018; Vyas et al., 2020).

2.4. Cells

Among the biological factors in cartilage tissue engineering, selecting the appropriate cellular source can play an important role in cartilage regeneration. Chondrocytes and mesenchymal stem cells have been used extensively to repair cartilage. In addition, other sources such as fibroblasts, stem cells, and genetically modified cells have been used in cartilage tissue engineering. Mature chondrocytes are extracted from a variety of sources, such as articular cartilage, nasal septum, rib cartilage, or ear cartilage. These cells have the ability to form cartilaginous ECM (Mekhileri et al., 2018). Adult mesenchymal stem cells are pluripotent cells that can produce different types of differentiated cells, including cartilage cells, fat cells, and osteoblasts (Simorgh et al., 2021). Mesenchymal stem cells have been isolated from various sources such as bone

marrow, muscle, adipose tissue, uterine endometrium, and tooth pulp (Arabpour et al., 2019). Since these cells usually do not express the core complexation molecules of class II histocompatibility (MHC-II) that are responsible for rejecting immunity, they can also be used as allogeneic cells (Dubin et al., 2019). In selecting MSCs as a cell source for cartilage repair, heterogeneity is the basic aspect of MSCs. The characteristics of different MSCs in cartilage regeneration should be considered. Recent studies showed that MSC functional heterogeneity leads to differences in the cells' potential for cartilage repair. This heterogeneity is caused by differences in donors, sources of tissues, and MSC subpopulations. Homogeneous isolation methods and cell culture systems can lead to differences in the results of the effectiveness of MSCs in cartilage repair (Zha et al., 2021).

Although many studies have shown promising properties of mesenchymal stem cells for cartilage tissue engineering, only a few human clinical trials have reported the use of mesenchymal stem cells with or without biological scaffolding for the joint. The results of these studies indicate the improvement of clinical symptoms in treated patients (Lee and Wang, 2017). Recent research has shown that the use of mesenchymal cells with their secretion of various agents such as PRP and exosomes, can initiate endogenous regenerative activities in the OA joint. Delivery of mesenchymal stem cells in scaffold-engineered structures is another approach to OA treatment (Song et al., 2020). Despite the development in this field, there are still challenges to developing MSCs for clinical use. One of these challenges is to identify useful therapeutic subpopulations from heterogeneous populations. It is also necessary to determine the effective dosage and administration method for clinical use (Tsiapalis and O'Driscoll, 2020).

2.5. Growth factor

The in vivo environment contains a combination of growth factors and different matrices that can help the process of cell differentiation and tissue repair and regeneration. Growth factors can play a key role in this process. Various growth factors are effective in cartilage regeneration, including bone morphogenic protein-6 (BMP-6), transforming growth factor-b3 (TGF-b3), and transforming growth factor-1 (IGF-1). Previous research has revealed that the simultaneous or separate use of these growth factors can regenerate and restore cartilage (Indrawattana et al., 2004).

Indrawattana et al (Indrawattana et al., 2004). showed that the simultaneous use of all three growth factors BMP-6, TGF-b3, and IGF-1 can be the type of growth factor together to induce cartilage more effectively. The combination of these growth factors, together with the use of a suitable scaffold or cell, can be a suitable method for the treatment of cartilage injuries.

2.6. Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) is an autologous and rich source of biologically active proteins and growth factors that play an important role in reducing inflammation, angiogenesis, cell migration, cell differentiation, and metabolism in pathological conditions including OA (Ramezanifard and Kabiri, 2017; Gholijani et al., 2022). According to previous research, this blood product has a positive effect on the repair process of tendons, ligaments, muscles, and bones. PRP in OA promotes cartilage repair by stimulating the proliferation of cartilage and mesenchymal stem cells. It also helps control inflammation by reducing pro-inflammatory mediators (Ramezanifard and Kabiri, 2017). Fick et al (Ficek et al., 2011). showed that PRP can improve the metabolic functions of damaged structures by inducing a regenerative response. Previous research has also shown a positive effect of this substance on cartilage regeneration and the proliferation of mesenchymal stem cells (Kabiri et al., 2014). Autologous blood products are very promising in tissue repair and regeneration, and positive results have been observed in various studies for PRP in knee OA compared to hyaluronic acid, and other intra-articular injections in musculoskeletal tissues. However, variables such as PRP preparation techniques, platelet concentration, molecular weight, OA intensity, dosage, and the number of injections lead to different responses. It is hoped that by controlling and managing these variables, a suitable treatment option can be provided to improve OA symptoms (O'Connell et al., 2019).

2.7. Exosomes

Exosomes mediate intercellular communication (Emami et al., 2020) and in the human joint are produced and secreted from sources such as chondroblasts, osteoblasts, synovial fibroblasts, and tenocytes. Recently, the potential of exosomes in the treatment of diseases such as OA has been increasingly considered (Ni et al., 2020). According to the findings, exosomes extracted from stem cells can protect against OA joint damage by stimulating cartilage repair and, synovitis inhibition and mediation. Research has shown that the use of BMSC-derived exosomes in the model of OA mice can effectively increase cartilage cell proliferation and migration and extracellular matrix synthesis, thereby leading to cartilage repair and reducing knee pain (He et al., 2020).

Recent studies have shown that exosomes extracted from synovial fibroblasts by delivering miRNA-126–3p to damaged cartilage tissue can control cartilage inflammation and cartilage degeneration and are a suitable option for treating patients with OA (Zhou et al., 2021). Chen et al (Chen et al., 2018). showed that the injection of exosomes derived from chondrocytes leads to increased collagen deposition and decreased vascular growth in engineered constructs and ultimately effectively facilitates cartilage formation. In this study, the produced cartilage was able to maintain its phenotype with minimal hypertrophy and vascular growth for up to 12 weeks. Also, exosomes derived from chondrocytes Cartilage progenitor stimulated the cell and increased the expression of cartilage markers (Chen et al., 2018). In another study, it was found that encapsulated exosomes remained in the joints longer after intra-articular injection than free exosome vesicles. Also, exosomes can reduce the progression of OA in the rat model by inhibiting cartilage-degrading proteases (Liang et al., 2020). But the use of exosomes as a new treatment strategy still faces challenges. The major challenges in this field are the protection of the effect of MSC-extracted exosomes on cartilage cells in the early stages of OA and the penetration of exosomes into the deep cartilage layer (Ni et al., 2020).

2.8. The immune system in OA: pathophysiology and therapeutics

The current mainstream thinking is that following initial injury to the skeletal system some cartilage and bone-specific auto-antigens will be exposed, which can trigger the activation of the innate and adaptive immune system (Haseeb and Haqqi, 2013). In joint disorders immune cells infiltrate the joint tissues, cytokines and chemokines are released from various kinds of joint cells, the complement system is activated, cartilage degrading factors such as matrix metalloproteins (MMPs) and prostaglandin E2 (PGE2) are released, resulting in further loss of the skeletal system (Lane Smith et al., 2000; Deng et al., 2021; Chen et al., 2020). Since available therapies for OA are not influential enough to manage disease (Chen et al., 2020), manipulation of the immune system might be a promising strategy to prevent OA development (Deng et al., 2021). Though, at present, no Immune-based therapies have been developed for the prevention or treatment of OA.

2.9. Macrophages

Importantly, both tissue-resident and non-tissue-resident synovial macrophages play a critical role in OA development (Chen et al., 2020; Bondeson et al., 2006, 2010). Accordingly, macrophages represent a major component (about 65%) of the joint-infiltrating immune cells in OA patients (Li et al., 2017; Rosshirt et al., 2021), and produce large amounts of cytokines following antigen encounter, which contribute to

the increased synthesis and release of many proteolytic enzymes from chondrocytes, which gives rise to the degradation of ECM components. Consequently, components of ECM act as DAMPs, which stimulate macrophage activation and increase synovial inflammation, resulting in a repeating cycle of inflammation and cartilage degradation (Bondeson et al., 2010; Zhang et al., 2020; Sakao et al., 2009). In order to control joint inflammation in OA, researchers used various strategies such as depletion strategy (Sun et al., 2016; Zhu et al., 2021) re-balancing the aberrant macrophages (Chen et al., 2020; Zhu et al., 2021; Wu et al., 2020a; Thomson and Hilkens, 2021; Lv et al., 2021; Zdziennicka et al., 2021; Sadtler et al., 2019; Badylak et al., 2008; Sridharan et al., 2018), targeting cytokines and chemokines in OA patients (Chen et al., 2020; Zhang et al., 2020; Zhu et al., 2021; Shen et al., 2011). Results from previous studies revealed that modifying macrophage function in OA patients could decrease the production of inflammatory factors, degradative enzymes, and growth factors to change the progression of OA disease. In sum, agents with immunomodulatory effects on macrophage reprogramming would be a potential therapeutic approach for the treatment of OA (Zhu et al., 2021).

2.10. Dendritic cells

Accumulating evidence has shown significant roles for dendritic cells (DCs) in the synovium of OA patients (Nefla et al., 2016). In the synovial fluid, mature DCs (mDCs) and plasmacytoid DCs (pDCs) were high in the synovial fluid of OA patients, suggesting that inflammatory mDCs and pDCs are involved in OA development and play a role in the inflammatory responses and increase in the concentration of MMP-1 in the synovial fluid (Hirohata et al., 2011; Jaiswal et al., 2020; Nie et al., 2019). It has been shown that increased TLR expression in DCs aggravates the inflammatory response to OA and may be a potential therapeutic target for effectively alleviating the progression of OA disease (Nie et al., 2019; Thwe et al., 2017; Damo et al., 2015). Inducing regulatory DCs (DC-regs) by gene manipulation of drugs is another approach to restrict inflammatory responses in the joints of an OA (Guo et al., 2018; Alahdal et al., 2021). More studies on the action mechanism of different DC subsets in OA are leading to the discovery of new treatment methods.

2.11. Natural Killer cells (NK)

NK cells are one of the main immune cell subsets infiltrating the synovium of patients with OA (Huss et al., 2010). NK cell-mediated cytotoxicity may play an important role in the regulation of inflammation and pathogenesis during OA (Białoszewska et al., 2013; Jaime et al., 2017). Up to now, there is still relatively little knowledge about the exact function of NK cells in OA. Hence there is a great need for research on the role of this cell in OA disease.

2.12. Neutrophils

Generally, serine proteases released by recruited neutrophils in inflammatory sites contribute to the damage of articular cartilage and subchondral bone remodeling (Wang et al., 2021). Two soluble mediators, synovial fluid elastase, are strong predictors of knee OA progression, reflecting a synergistic role of neutrophils in the pathogenesis and worsening of OA (Hsueh et al., 2021). In contrast, neutrophils by activating the expression of genes that control the anabolism of chondrocytes, promote the accumulation of ECM and enhance the protection of the cartilage (Deng et al., 2021; Headland et al., 2015). Altogether, more study of neutrophils' role in OA pathogenesis is needed to find an effective therapeutic approach for this disease.

2.13. T cells

Significant abnormalities in the T-cell profile have been found in the peripheral blood, synovial fluid, and synovial membranes of OA patients (Li et al., 2017). Cytokines secreted by different T cell subsets have various impacts in the OA context. Given that, some cytokines secreted by activated T cells can promote the induction of osteoblasts and osteoclasts (Stanley et al., 2006) while others inhibit the maturation of osteoblasts and osteoclasts (Maruotti et al., 2017; Croes et al., 2016). As T cells have a major role in the pathogenesis of OA, T cell immunotherapies might be a suitable approach for this disease (Wheeler et al., 2020).

2.14. Immune regulation of Chondrocytes

Chondrocytes occupy 1–5% of cartilage tissue. In normal circumstances, various growth factors and enzymes are produced by these cells to regulate extracellular matrix (ECM) synthesis (Chen et al., 2021), however; as such in disease conditions such as OA, chondrocytes contribute to cartilage destruction by shifting toward a degradative and hypertrophy-like state (Ball et al., 2022). Of note, metabolic alterations have been seen in chondrocytes in OA, which contribute to an increase in catabolism and apoptosis (Zheng et al., 2021). Importantly, numerous cytokines and cellular signals form an interactive network to regulate chondrocyte function and maintain cartilage homeostasis (Kozhemyakina et al., 2015; Liu et al., 2017; Fischer et al., 2018).

As mentioned earlier, the immune system plays an important role in OA pathogenesis. Both arms of the immune system are involved, however; the role of innate immunity is more prominent in the modulation of tissue homeostasis (Li et al., 2021a). Interestingly, DAMPs released upon tissue injury can be recognized by pattern recognition receptors (PRR), such as TLR and NOD-like receptors (NLR) (Barreto et al., 2020). Consequently, inflammatory pathways may be initiated by resident and recruited cells (Li et al., 2021a). Noteworthy, neutrophils are among the first cells that are recruited to the site of injury. These cells, in turn, produce pro-inflammatory mediators and elastase and are capable of recruiting macrophages, DCs, and NK cells. They also induce chondrocyte apoptosis and ECM degradation (Li et al., 2021a). Following activation, NK cells produce interferon-γ (IFN-γ) which polarizes infiltrating macrophages into M1 macrophages. In contrast to M2 macrophages, M1 macrophages secrete pro-inflammatory mediators that interfere with cartilage repair (Li et al., 2021a).

In addition to innate immune cells, CD4 + T cells including Th1 (T helper), Th2, Th17, and Tregs are also recruited to the site of inflammation. Th1 cells and Th17 cells release inflammatory factors that act on chondrocytes and inhibit proteoglycan production, thus inhibiting cartilage repair (Pacquelet et al., 2002). Th2 cells produce anti-inflammatory cytokines and activate B cells. B cells, in turn, release several pro-inflammatory factors, including IL-1β, IL-6, and TNF-α, to stimulate chondrocyte death and cartilage matrix breakdown (Lin et al., 2018). Furthermore, Tregs diminish inflammation and induce the production of anti-inflammatory mediators by neutrophils, which in an indirect manner, promote cartilage repair (Li et al., 2021a). Importantly, OA chondrocytes represent phenotypic plasticity in response to various stimuli (Pemmari et al., 2021). This phenotypic plasticity may lead to the identification of new therapeutic avenues for the development of treatments for OA. Of interest, exploring the exact mechanism of interaction between chondrocytes and immune cells needs further investigation (Pereira et al., 2016).

2.15. Pharmacologic treatments

Pharmacologic modalities for arthritis treatment based on American College of Rheumatology (ACR) recommendations include topical cream, nonsteroidal anti-inflammatory drugs (NSAIDs), steroidal drugs, and complementary medicines.

Capsaicin cream is considered for joint pain. Capsaicin is a component of chili peppers that can warm and make neurons desensitized by P selectin deletion. It can increase the risk of skin ulcers in older diabetic

patients (Altman and Barthel, 2011). NSAIDs and acetaminophen are the mainstays for arthritis. The second line of treatments with this group of treatment belongs to COX-2 inhibitors. All these drugs have side effects that limit their application. Gastrointestinal, hepatic, and cardiorenal adverse effects increase dosage and treatment duration (da Costa et al., 2021). Intra-articular injection of steroid-like corticosteroids works as an anti-inflammatory agent. They can reduce pain and disease symptoms but side effects limit their application (Cheng et al., 2012). Nanoparticles with controllable size to direct intra-articular injection are another option that opened a new horizon to OA treatment. Biodegradable, high stability, hydrophilic and hydrophobic substances incorporation, and different administration route are advantages of nanoparticles. Nanoparticles can carry drugs on their surface or protect them from enzymatic degradation and improve drug penetration through the cartilage matrix (Ghadi et al., 2014; Li et al., 2021b).

Some studies showed an intra-articular injection of hyaluronic acid or its derivatives that is called viscosupplementation improves the function of the joint after weeks, but the risk of reaction limits its usage and it should be individualized for each patient (Tapasvi et al., 2019).

2.16. Nonpharmacologic modals

Based on the ACR recommendations depending on the patient's comfort level and preferences both land-based and aquatic-based activities are recommended. Because it has been approved that physical activities reduce pain and improve function in these patients (Lund et al., 2008; Vignon et al., 2006). One of the Chinese martial arts is Tai Chi which includes some slow and precise movements that have health benefits. Pain and stiffness reduction has been seen in a pilot cluster-randomized trial (Vignon et al., 2006). Also, there are some devices like walking canes, braces, and appropriate footwear that can improve a patient's ability to perform routine activities. Teaching patients such techniques as joint protection and energy conservation can prevent further injury. Other Non-pharmacologic options are pulsed electromagnetic field stimulation devices and transcutaneous electrical nerve stimulation (TENS), which are noninvasive approaches in physiotherapy and extensive studies have been conducted on their effects on OA. These techniques are usually used to relieve acute and chronic pain in patients (Vance et al., 2012). Acupuncture therapy is another method to decrease pain in these patients, especially in combination with pharmacology treatment options. Balneotherapy (Spa therapy), magnetotherapy, Glucosamine sulfate, and glycosaminoglycans are other options that had shown limited improvements in some studies (Vance et al., 2012; Ragle and Sawitzke, 2012; Boada-Pladellorens et al., 2021; Verhagen et al., 2015). Additional to the above-mentioned methods some recommendations may be useful in these patients such as aerobic land exercises, lifestyle-changing like losing weight for overweight patients, psychosocial interventions, and self-management programs (Wellsandt and Golightly, 2018).

2.17. Cell therapy

Also, there are new high-tech procedures that can help cartilage repair. One of them is autologous chondrocyte implantation that now advanced to matrix-associated autologous chondrocyte implantation (MACI). MACI is a two-stage procedure in which autologous cells are harvested from the patient's cartilage, then seeds in a collagen matrix. This mixture is re-implanted into the cartilage defect. MACI showed a clinical improvement at long-term follow-up (Gille et al., 2016).

Autologous matrix-induced chondrogenesis (AMIC) is another option for cartilage defects that is a single-stage procedure. In this method, some microfractures would be created in the wound area and the whole defect covered by a cell-free collagen matrix (Benthien and Behrens, 2010). It has been shown the AMIC procedure with a suitable rehabilitation protocol, can be considered an adequate alternative for the treatment of cartilage defects (Tradati et al., 2020).

A new technique to help the regeneration of cartilage is to remove neighboring senescent cells. Senescent chondrocyte accumulation around the cartilage defect has a relation with the development of arthritis, clearance of these cells can attenuate arthritis development (Jeon et al., 2017).

2.18. Gene therapy

The first attempt to deliver genes to articular tissue was described in 1993 (Bandara et al., 1993). They performed the study on 9 patients and revealed that gene therapy is safe and feasible. Gene therapy for cartilage requires potentially useful cDNAs such as TGFβ, IGF-1, FGF, and EGF and factors to maintain and support cartilage matrix like collagen type II, and cartilage oligomeric matrix protein (COMP). Also, it needs signaling components such as Hedgehog and inhibitors of apoptosis and senescence as Bcl-2 (Robbins et al., 1999; D'Lima et al., 2001).

Generally, there are two modes of intra-articular gene delivery: direct in vivo mode: and direct gene delivery to joint space. This method is simpler and cheaper but has safety limitations, and the second mode is the ex vivo approach: genetic manipulation of cells in the laboratory and turning back to the body. This approach is more invasive and expensive but safer (Steinert et al., 2008). Method selection is depending on some conditions like the gene to be delivered and the vector used. Carriers that are used in ex vivo or in vivo approaches are adenovirus, herpes simplex virus, adenoassociated virus vectors (AAV), lentivirus, and nonviral vectors. AAV catches more attention because it can penetrate the depth of cartilage and transduce chondrocytes in situ. The main point in gene delivery to the articulation is to release cDNA-encoding products that cause maintaining, endogenous production of gene products in the damaged area (Rodriguez-Merchan and Valentino, 2019). Kim and colleagues 2018 performed a phase III clinical trial with Tissue Gene-C (TG-C), a cell and gene therapy for OA consisting of non-transformed and transduced chondrocytes. They showed that TG-C has a significant improvement in OA patients but there are some complications such as edema, articular swelling, and pain in the injection site (Kim et al., 2018).

2.19. Surgical techniques

The last line of treatment in patients with OA is surgical treatment. Surgical treatment includes various interventions. The arthroscopic procedure detects chondral lesions. Loose parts of the lesion can be removed with this method (Mor et al., 2015), but this procedure only causes pain relief in patients and it does not prevent the progress of the OA (Rönn et al., 2011) and the remaining cartilage would be susceptible to degeneration (Jamil et al., 2018). Microfracture is another common interventional procedure that penetrates subchondral bone and allows bone marrow to fill the injury site. Bexkens and colleagues in their study have shown about 60% of patients showed improvements and turned back to sports (Bexkens et al., 2017). Mosaicplasty or osteochondral autologous transplantation is another interventional procedure in that osteochondral plugs are harvested from a suitable area and transferred to the defective place. Site morbidity, poor integrity, and degeneration over the long term are weak points and side effects of this method (Martín et al., 2019). Osteotomy is performed for young patients whose OA is limited to one compartment but total arthroplasty is considered for elderly patients with Progressive OA (Rönn et al., 2011).

3. Conclusion and future perspective

Based on the evidence from this review article no single treatment can be recommended for the treatment of osteochondral defects. In the approach to the treatment of AO, based on severity, the progress of the disease, and the patient's situation it has been recommended to apply more than one procedure to achieve better results (Sacks et al., 2018). New achievement in OA pathogenesis brings better knowledge of the

disease and future treatments absolutely would be those that target cartilage molecular processes (Cai et al., 2021). In addition to traditional treatment methods cell therapy, chondrocytes, and stem cells would be another option but the lack of standardization of the method has not been resolved. Hydrogel in combination with stem cells creates a new opportunity for cell therapy in OA. Cells in the hydrogel are distributed and extended in 3D as in native cartilage. In another hand, the controlled release of biomolecules from stem cells is an additional advantage (Wu et al., 2020b). Gene therapy is another novel way to solve OA challenges that can create long-lasting targeted and in-situ proteins. Preclinical studies revealed its efficacy and safety (Evans et al., 2018).

Every therapy method has its own merits and demerits in the approach of OA. Till now there is no single treatment to create native cartilage in joints and as has been earlier mentioned a combination of some procedures have been applied to prevent deterioration of the disease progress.

Data Availability

No data was used for the research described in the article.

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