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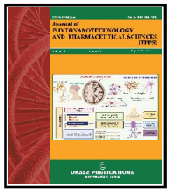

Review Article : Open Access

Innovative treatments for osteoarthritis: A holistic approach

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Abstract

Osteoarthritis (OA) is a common degenerative joint condition that causes pain, stiffness, and limited movement due to cartilage degradation. The main focus of traditional OA therapies has been on managing symptoms with pharmaceuticals such as analgesics and nonsteroidal anti-inflammatory medications (NSAIDs) or with surgery like joint replacement. Recent developments; however, have prompted the creation of novel, all-encompassing strategies meant to treat the disease's underlying causes as well as its symptoms. To promote cartilage regeneration and reduce inflammation, this review examines a variety of novel therapeutics, including regenerative medicine methods including stem cell therapy and platelet-rich plasma (PRP) injections. Furthermore, the importance of lifestyle adjustments is stressed, including customized exercise regimens, managing weight, and nutritional therapies, as essential elements of an all-encompassing therapy strategy. Combining complementary treatments with herbal medicine, acupuncture, and yoga opens up new possibilities for joint function and pain alleviation. A more comprehensive approach to managing osteoarthritis can be reached by fusing these cutting-edge therapies with conventional medical practices, which may improve patient results and quality of life. This holistic approach underscores the importance of personalized care, taking into account the unique needs and conditions of each patient, and suggests a shift towards more integrative, patient-centred treatment models in osteoarthritis management.

1. Introduction

The Greek words osteon, which means “of the bone,”arthron, which means “joint,” and “itis”, which means “inflammation,” are the sources of the English phrase “osteoarthritis.” The most prevalent kind of arthritis affects the global ageing population. Prolonged pain and reduced function are linked to osteoarthritis Fox *et al*. (2009).The two main types of chronic arthritis are (i) hypertrophic arthritis, which is defined by focal loss of cartilage with little evidence of the typical form of inflammation (it is not a systemic disease and the “inflammatory component”seems to be restricted to the cartilage and bone) and by growth (hypertrophy) of the adjacent bone and soft tissue (*i.e.,* osteoarthritis (OA), (ii) atrophic arthritis, which is characterized by synovial inflammation and erosion or atrophy of the cartilage and bone (*e.g.,* rheumatoid arthritis (RA) (Attur *et al.,* 2002). Although, an epidemiology study indicated that only 8.9% of adults had clinically severe OA of the hip, hand, or knee, it has been noted that around one-third of adults exhibit radiologic indications of OA (Felson *et al*.,1998). Knee OA was the most frequent kind of OA, occurring in 6% of persons (Andrianakos *et al*., 2006). The degenerative joint condition known as osteoarthritis (OA) is typified by a build-up of mechanical forces on joints that eventually result in the articular cartilage being destroyed.The process of cartilage ECM degradation has been linked to certain members of the matrix metalloproteinase (MMP) and disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) gene families; other contributing factors include: (i) increased extracellular matrix (ECM) degradation; (ii) decreased ECM production; and (iii) chondrocyte death (Okada *et al.,* 2009). NSAIDs and glucocorticoids are two common medications used to treat osteoarthritis (OA); yet, none of these treatments isperfect, and they are all linked to side effects. Recently, novel approaches have been put forth, including stem-cell therapy, gene therapy, anti-cytokine therapy, growth factor administration, and new lubricant agents such as lubricin (Chevalier *et al.,* 2010).

In the Western world, osteoarthritis (OA) is a major cause of discomfort and disability and is one of the most prevalent recurrent debilitating joint illnesses (Comblain *et al.,* 2016). The entire joint is affected by osteoarthritis (OA), a degenerative, progressive, and chronic condition that is marked by bone and cartilage degradation, subchondral bone structural abnormalities, and destruction of the protecting articular cartilage (Kumar *et al*., 2015). This persistent joint ailment affects about 10% of the whole population, with women between the ages of 50 and 60 being particularly affected. In people over 65, it is the primary cause of disability and as people age, the prevalence of arthritisand other chronic joint complaints rises (Lawrence *et al.,* 2008).Three symptoms of decreased function, stiffness, and persistent knee pain as well as three signs of limited movement, crepitus, and bony enlargement, are commonly used to diagnose knee OA (Zhang *et al.,* 2009).

2. Pathophysiology and mechanism of action of osteoarthritis

Considering its complexity, the initiation, progression, and severity of OA are each driven by a plethora of factors. Furthermore, in all

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individuals, OA does not progress at a similar rate. At the cartilage-bone interface, an inverse relationship between subchondral bone changes and articular cartilage degeneration has been reported. As the subchondral bone thickens, a higher stage of cartilage degeneration is observed (Bobinac *et al.,* 2003). Earliest pathological changes in OA are commonly seen on the articular cartilage surface, with fibrillation occurring in focal regions experiencing maximal load.

The proliferation of chondrocytes, the only cell type present in cartilage, dramatically accelerates in response to the loss of matrix. Some chondrocytes undergo a phenotypic change to hypertrophic chondrocytes, which is similar to the cells found in the growth plate's hypertrophic zones. As OA progresses, extensive matrix degradation and loss occur due to the continuous production of proteases driven by proinflammatory cytokines, which stimulate chondrocytes to produce more cytokines and proteases in an autocrine and paracrine manner, the bone changes in OA include subchondral sclerosis due to increased collagen production, with osteophyte formation and bone cysts at more advanced stages.

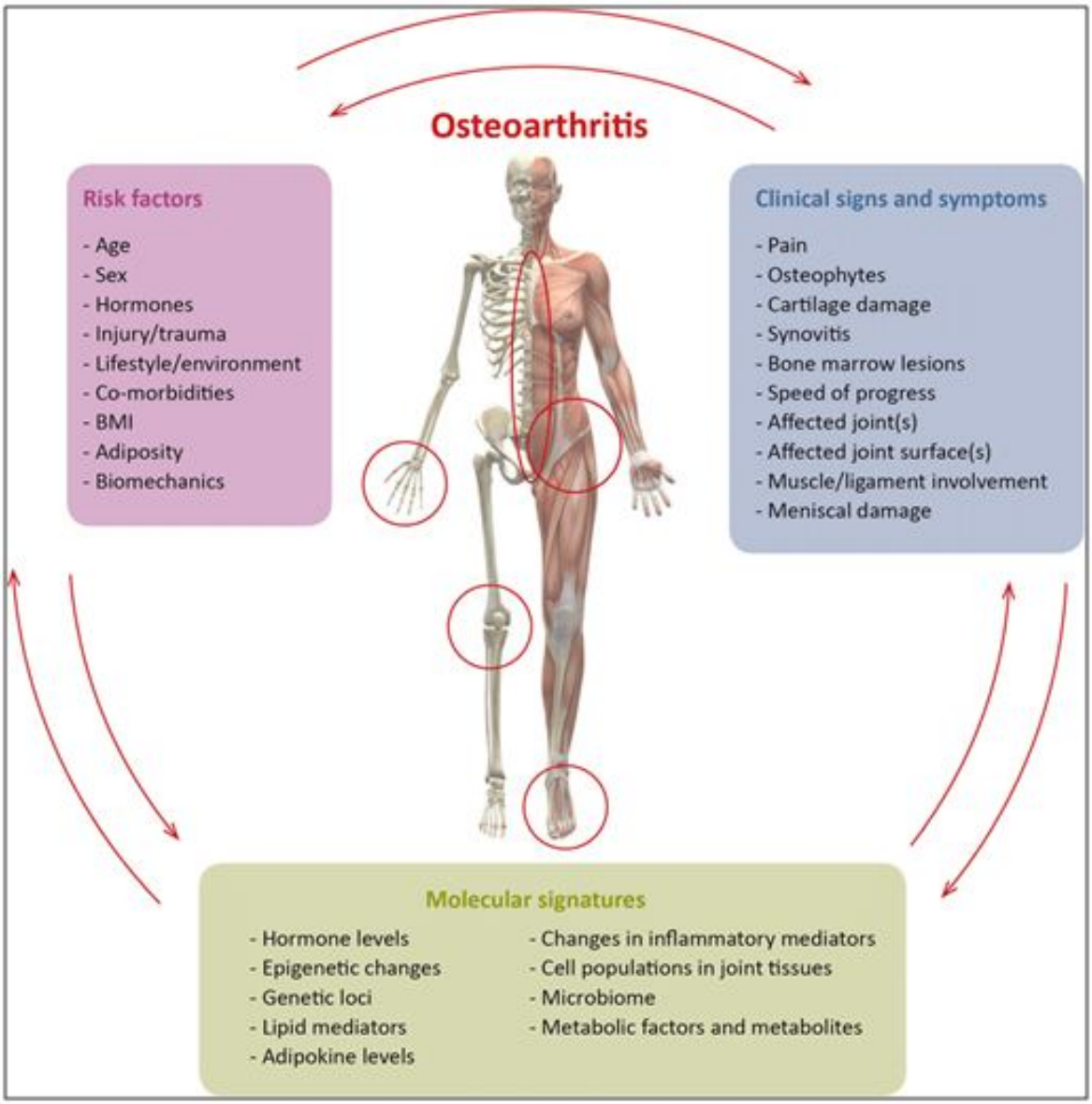

Figure 1: Risk factors and symptoms of osteoarthritis (Mimpen *et al.*, 2019).

Osteophytes have been described as bone and cartilage outgrowths occurring at the joint area. The direction of osteophyte growth is sensitive to the size and local cartilage narrowing, except for the lateral tibia and medial patella (Nagaosa *et al.,* 2002). Biomechanical factors support osteophyte development. Most patients withsymptomatic OA exhibit synovial inflammation and hypertrophy (Baker *et al.,* 2010). However, synovitis inflammation is not the triggering factor for primary OA but contributes to the progression of pain and disease (Wang *et al.,* 2018). Plain radiographs underestimate the joint tissue involvement in OA since they only visualize a component of the condition including

cartilage loss that results in joint space narrowing and bony changes that result in subchondral sclerosis, cysts, and osteophyte formation. Once these changes are apparent on radiographs, the condition has significantly advanced (Loeser *et al.,* 2012).

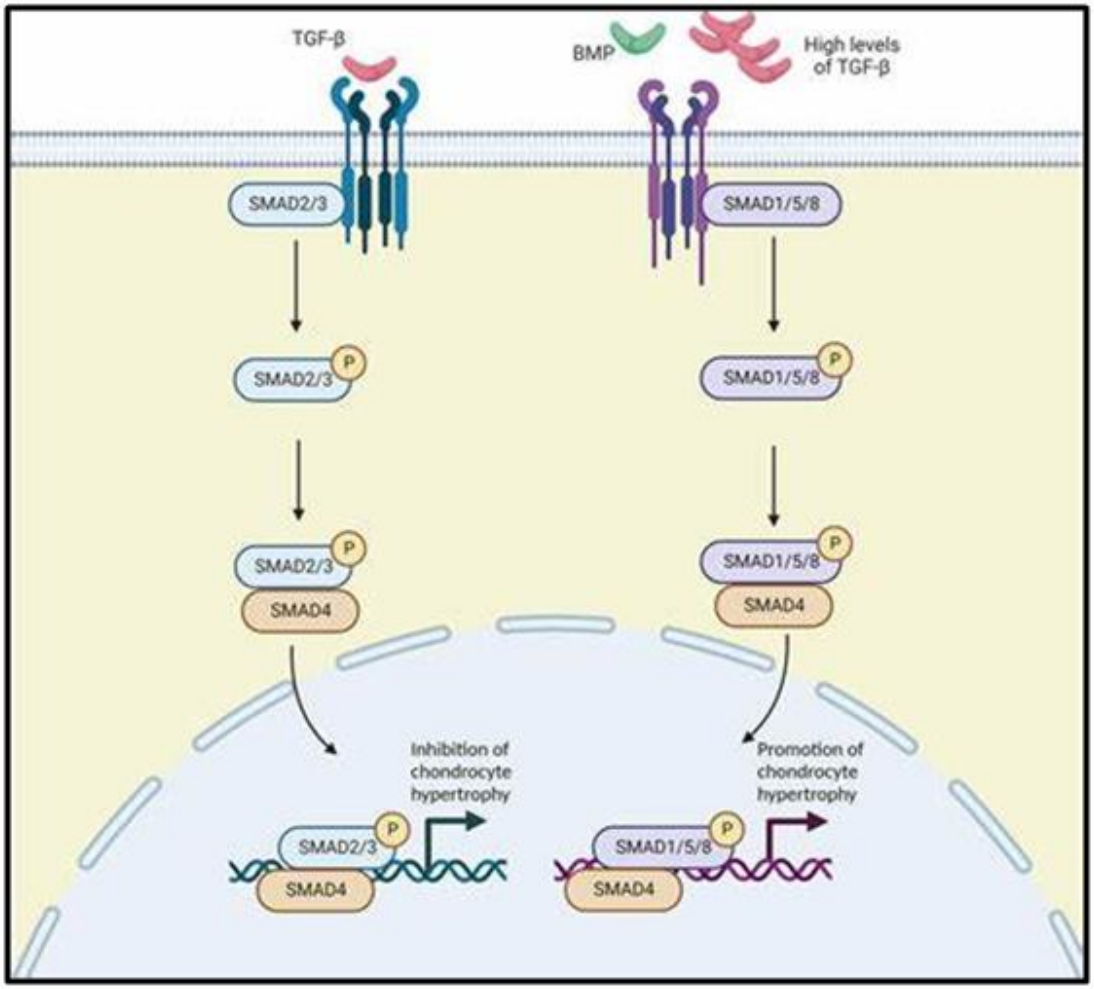

Figure 2: Pathophysiology of osteoarthritis (Poulsen *et al.,* 2023).

Magnetic resonance imaging (MRI) studies can detect early disease and have provided evidence of matrix changes in cartilage, synovitis, bone marrow lesions, and degenerative changes in soft-tissue structures beyond the cartilage including ligaments and the knee menisci (Sharma *et al*., 2014). The arthroscope can play an important diagnostic role in patients with unexplained knee pain and swelling or in patients with established knee arthritis whose symptoms are disproportionate to radiographic findings (O'Rourke *et al*., 1994).

3. Evaluation criteria

As OA is a clinical diagnosis, it can be made with confidence if any of the following conditions hold: (i) pain that gets worse with movement and gets better with rest; (ii) older than 45 years; (iii) stiffness in the morning that goes away in less than 30 min; (iv) expansion of the bony joints; and (v) restricted range of motion. Among other soft tissue abnormalities, a differential diagnosis should include rheumatoid arthritis, psoriatic arthritis, crystalline arthritis, hemochromatosis, bursitis, avascular necrosis, tendinitis, and radiculopathy (De Laroche *et al.,* 2018).

Blood tests that are typically normal in OA include CBC, ESR, rheumatoid factor, and ANA, albeit they may be requested to rule out inflammatory arthritis. A diagnosis of osteoarthritis (OA) is consistent with a white blood cell count of less than 2000/microl, mostly mononuclear (non-inflammatory) cells, if synovial fluid is available. Radiographic abnormalities, such as marginal osteophytes, joint space constriction, subchondral sclerosis, and cysts, can be seen on X-rays of the afflicted joint. However, these findings are not correlated with the severity of the disease and may not be evident at the beginning of the illness (Ackerman *et al.,* 2017). MRI is not always recommended for the workshop of OA.

4. Treatment /Management

Reducing pain and functional loss are the two main objectives of OA treatment. Both pharmacologic and non-pharmacologic therapy are part of a comprehensive care strategy for the condition. Patients with less severe symptoms may usually be treated with the former, while more advanced conditions require a mix of the two (Kriz *et al.,* 2018). Key components of non-pharmacologic therapy are: (i) avoiding activities that aggravate the joint or cause it to become overworked; (ii) strengthening exercises; (iii) losing weight; and

(iv) occupational therapy, which uses braces, splints, canes, or crutches to relieve joint stress. Losing weight is a crucial strategy for those who are overweight or obese since every pound lost can result in a three- to six-fold reduction in the load over the knee.

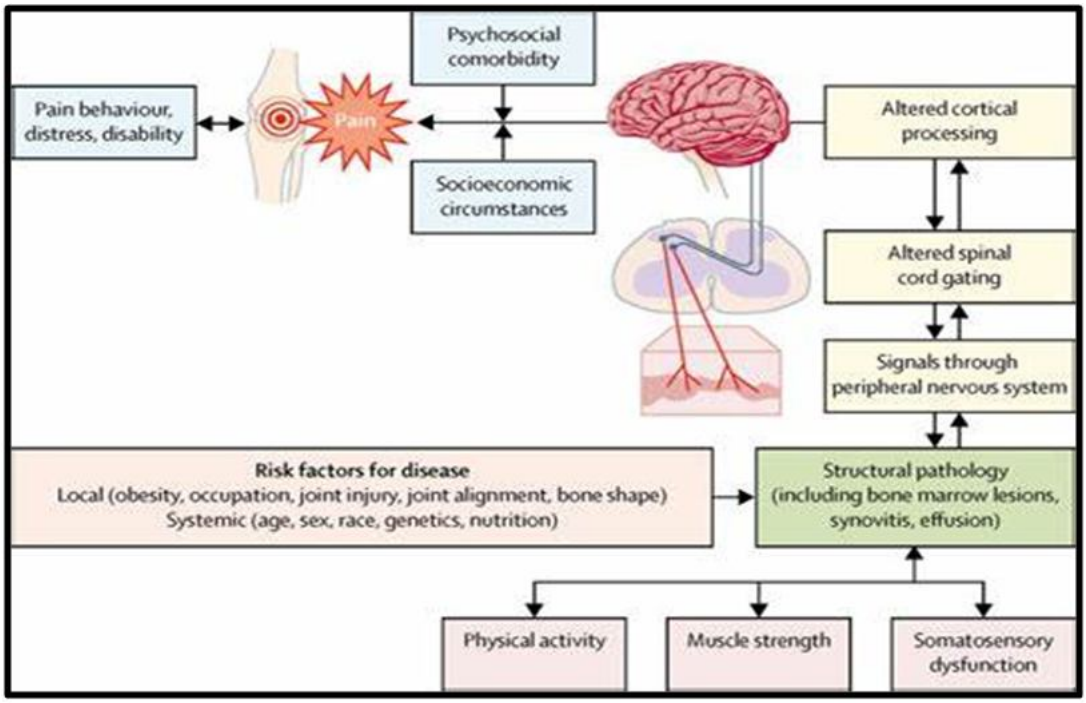

Figure 3: Clinical assessment for osteoarthritis (David *et al.*, 2019).

Instructing patients on exercises and helping them use equipment like canes correctly are two things that formal physical therapy can greatly help with. Physicians should routinely recommend exercise regimens that incorporate both resistance and aerobic training since they have been demonstrated in numerous trials to reduce pain and enhance physical function (Di Laura Frattura *et al*., 2018). NSAIDs are often administered topically or orally; topical NSAIDs have fewer gastrointestinal and other systemic adverse effects but are less effective than their oral equivalents. Another useful therapy for OA is intraarticular joint injections, particularly when there is severe discomfort. The response to glucocorticoid injections varies, and repeated doses are still a topic of debate (Xing *et al.,* 2018). Injections of hyaluronic acid are an additional alternative, however, there is debate regarding their superiority over placebo. Duloxetine is not very effective for OA.

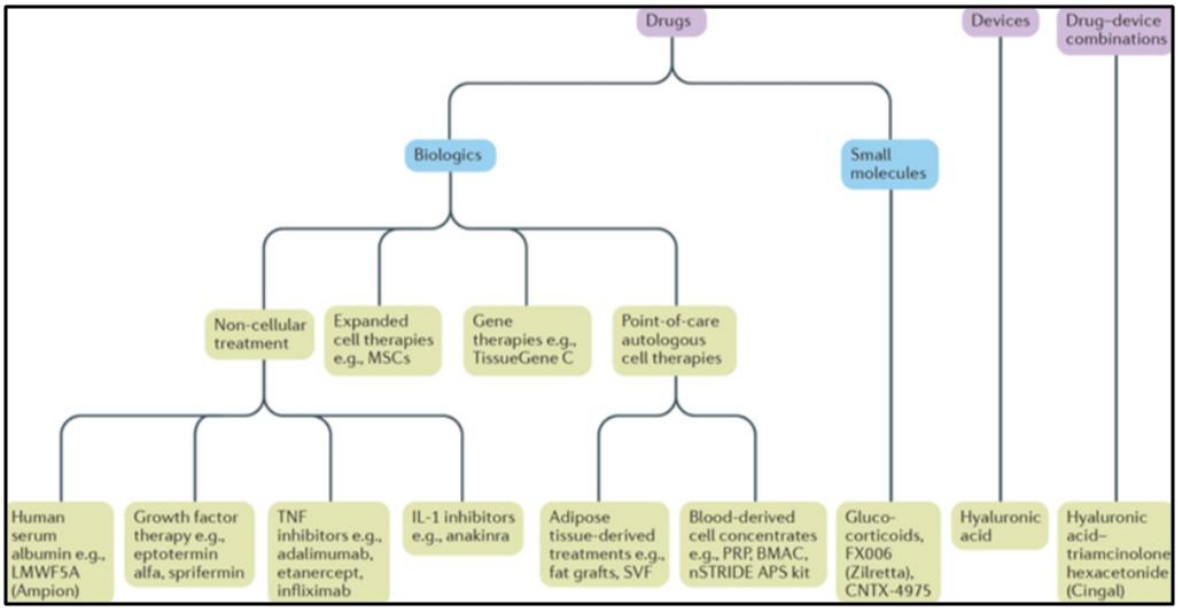

Figure 4: Types of treatment for osteoarthritis (Jones *et al.*, 2019).

5. Current research

5.1 Recent approaches for cartilage regeneration

Recent developments in cutting-edge domains like osteoarthritis cartilage regeneration rely on scaffold-based and nanotechnology-based electrostatic techniques as well as a cell-basedstrategy that includes gene insertion and some bioactive substances like PRP.

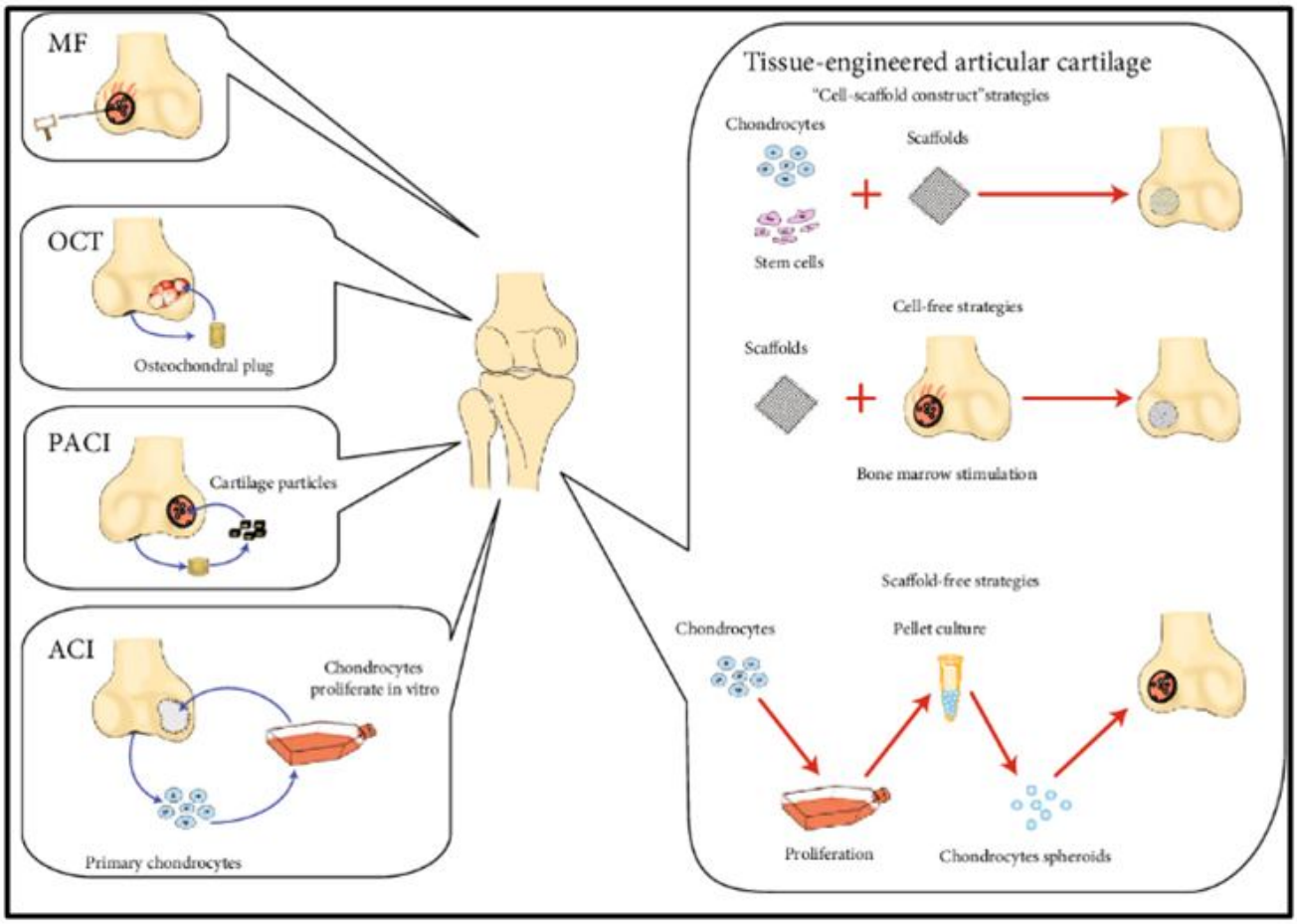

Figure 5: Approaches for cartilage regeneration (Householder *et al.*, 2023).

a. Cell-based therapy for cartilage regenerative

To repair damaged cartilage in joints, cells can be used as therapeutic agents. Chondrocytes and mesenchymal stromal cells from diverse sources are the main cell types employed in the treatment of chondral and osteochondral abnormalities (Huang *et al*., 2016). Before implanting, the approach necessitates isolating and expanding the cells ex vivo in a monolayer culture. After passaging in culture, chondrocytes frequently lose their ability to form extracellular matrix (ECM) and proliferate; this process is known as de-differentiation (Goldring *et al*., 1986; Schnabel *et al.,* 2002). Perlecan, a heparin sulphate proteoglycan, has been found in recent research to have a significant role in the healing of human cartilage defects. Additionally, the authors show that heparanase treatment of the chondrocytes enhanced their ability to proliferate and the production of chondrogenic genes, which may have consequences for the growth of cells *in vitro* (Garcia *et al*., 2021).

To successfully promote cellular proliferation and ECM expression, bioreactor culturing has recently been created (Brenner *et al*., 2014). It has been demonstrated that the overlaying of self-assembled MSCs on top of hydrogel scaffolds loaded with chondrocytes promotes cell-mediated regeneration of hyaline-like cartilage (Mesallati *et al*., 2017). By implanting a collagenous patch containing slowly-released BMP-2 sutured onto the inner synovial membrane trans-cutaneously, a novel technique was recently developed to generate cartilage for grafting in vivo from endogenous chondrogenic-differentiated stem cells, avoiding the ex-plantation of healthy cartilage (Hunziker *et al*., 2015). Because chondrocytes can produce collagen II and ECM, they are an excellent choice for the seed cells in cartilage TET. Nevertheless, when cultivated *in vitro*, they may lose their chondrogenic character.

Furthermore, the source of instability and the smaller and less homogeneous chondrocytes from older patients significantly reduced their potential to regenerate further. Fortunately, because of their accessibility and low immunogenicity feature, stem cells-including MSCs, embryonic stem cells, and induced pluripotent stem cells (iPSCs)-are becoming more and more popular among researchers for the treatment of AC defects, such as localized chondral lesions (Harrell *et al.,* 2019). BMSCs continue to be the most effective among them

for AC and bone TET or regenerative medicine. However compared to BMSCs, adipose-derived mesenchymal stem cells (ADSCs) are thought to be a useful substitute since they have some benefits and comparable characteristics (Bionaz *et al*., 2015).

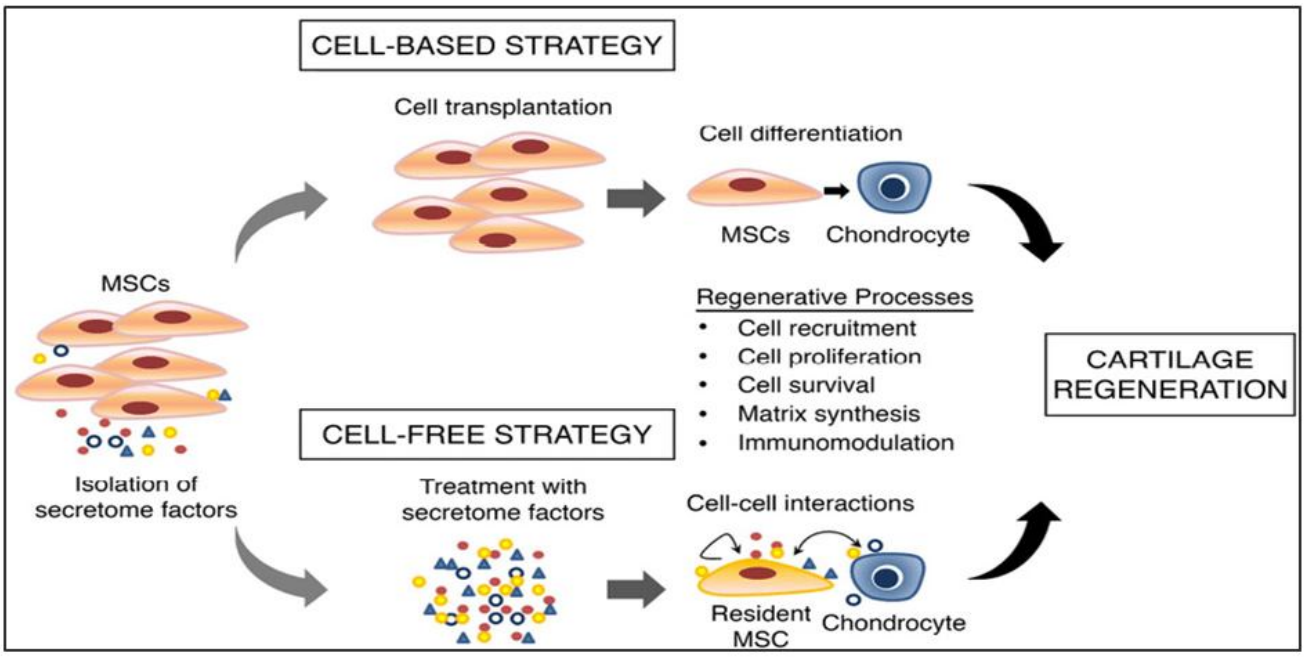

Figure 6: Cell-based and free strategy in cartilage regeneration (Toh, 2017).

b. Cell-free strategy (MSCs derived exosomes)

There are now several sources of stromal cells accessible for cartilage repair. This is because they can create structural and functional hyaline extracellular matrix (ECM) molecules, which allows them to multiply in culture and differentiate in a directed manner. Additionally, they can produce a variety of anti-inflammatory, antiapoptotic andimmunomodulatory substances that promote healing. Numerous studies have shown that using adult bone marrow-derived MSC to repair cartilage damage is beneficial. Similar to bone marrow-derived stem cells, but easier to extract, with more cell density, and more proliferation, adipose-derived stem cells (ASC) have also attracted interest. Muscle, synovial membrane, trabecular bone, dermis, blood, umbilical cord blood, and periosteum are other sources of stem cells being studied for cartilage regeneration (Jiang *et al.,* 2021). Several issues still exist, such as stem cell heterogeneity and early differentiation during *in vitro* growth, despite the numerous effective uses in cartilage regeneration (Filardo *et al.,* 2016).

It was demonstrated that genetically altered cells might enhance cartilage repair. It is possible to produce transfected genes that induce chondrogenic differentiation, hyaline matrix production, and release of pro-inflammatory proteins during differentiation. Gene transfection can occur *ex vivo* or *in vivo*, systemic or local. It is essential to make sure the surgery is safe since cartilage injuries do not pose a serious risk to life (Steinert *et al.,* 2018). The application of the stem cell "niche" in the form of concentrates like bone marrow concentrate (BMC) and adipose tissue's stromal vascular fraction (SVF) has also gained traction in recent years in the field of articular cartilage regeneration research. Based on histological immunohistochemical and molecular analyses, an extracellular matrix (ECM) resembling cartilage was formed (Cavallo *et al.,* 2013). Early on, it appears that MSC's capacity to differentiate into multiple cell types was primarily responsible for its therapeutic effects. Subsequently, it became clear that their secretome-which allows them to release certain GF and chemokines-plays a part. MSCs release bioactive substances that promote angiogenesis, blood flow, and the mitosis of progenitors unique to a given tissue, while also preventing apoptosis and the development of fibrosis or scarring at the site of damage.

Additionally, they release immunomodulatory substances that stop chronic inflammatory processes and T-cell surveillance. Based on its composition of trophic agents (chemokines, cytokines, hormones, and lipid mediators) with paracrine effects on the cells of the local microenvironment, the secretome's utility for tissue regeneration increased (Murphy *et al.,* 2013). MSCs have a paracrine effect that extends beyond their ability to produce soluble substances; they also produce a large number of extracellularvesicles (EVs) (Darrigo *et al*., 2019). In addition, they exhibit anti-inflammatory, proangiogenic, antiapoptotic, and antifibrotic properties. Certain mRNAs or micro RNAs can be produced by EVs from tissue-damaged cells to reprogram the phenotypic of stem cells.

Tissue-damaged cells can be reprogrammed by EVs generated by the resident or circulation-recruited MSCs through the induction of de-differentiation, the creation of soluble paracrine mediators, and the start of these cells' cell cycle, all of which promote tissue regeneration (Rani *et al*., 2015). Because MSCs may develop into chondrocytes and are simple to harvest with little donor site morbidity, they present a viable cell source for cartilage lesion regeneration and repair (Park *et al.,* 2018). The MSCs can be injected intraarticularly or can be transplanted into the defect after a surgical incision, depending on the particular cartilage disease. According to the International Cartilage

Repair Society criteria, 76% of the patients in post-surgical prognostic research evaluating the effectiveness of AT-MSC implantation for cartilage defects had their repair assessed as abnormal or seriously abnormal (Koh *et al*., 2014).

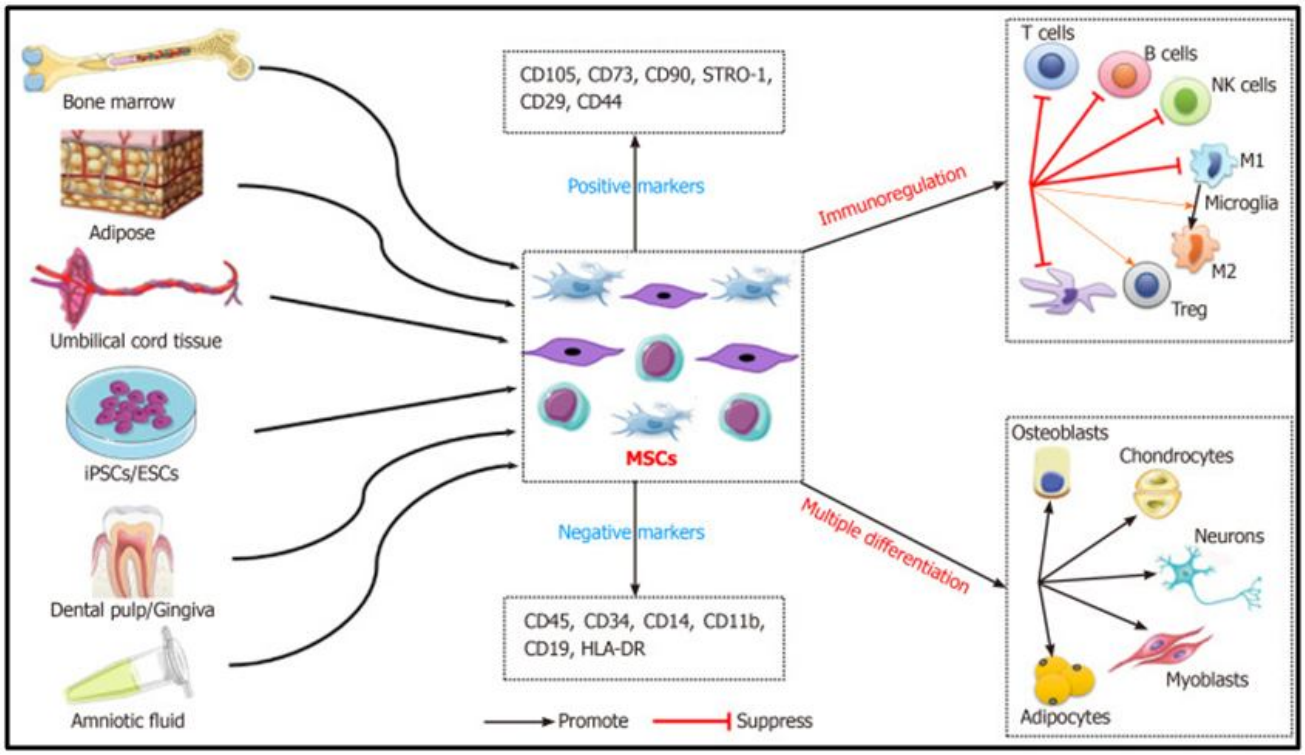

Figure 7: Mesenchymal stem cells in cartilage regeneration (Ma *et al*., 2020).

c. Scaffold-based therapy

The formation of three-dimensional (3D) tissue is sustained by scaffolds. Their status, content, and structure are different. The perfect scaffold should promote cell adhesion, development, and differentiation and be biomimetic, biocompatible, biodegradable, and non-immunogenic. It should get integrated into the lesion site after implantation and aid in the healing process. It should also be affordable and simple for surgeons to use. Both natural and synthetic scaffolds can be used for cartilage regeneration (Wasyleczko *et al*., 2020). High levels of bioactivityand biocompatibility are found in natural materials. However, show poor mechanical stability because of their rapid hydrolysis.

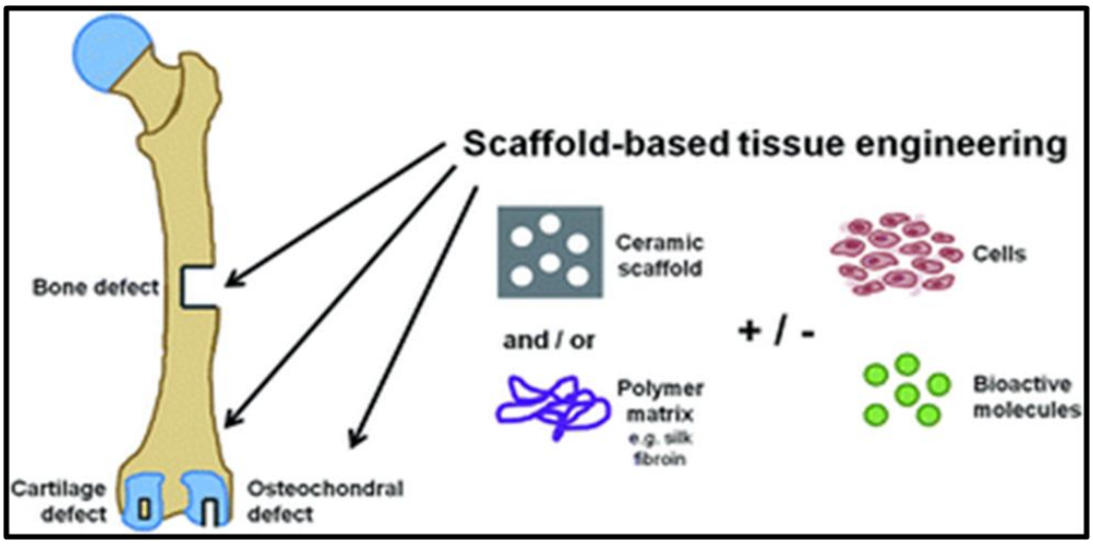

Figure 8: Scaffold-based cartilage regeneration (Kumar *et al*., 2019).

Table 1: Advantages and disadvantages of naturally occurring scaffolds

Natural origin scaffolds	Advantages	Disadvantages
Hyaluronic acid	Anionic, non-sulfated glycosaminoglycan (GAG) is present in cartilage ECM. Supports cell attachment through surface receptors like CD44ECM.	Poor mechanical properties, rapid degradation
Chondroitin sulfate	Sulfated GAG is present in cartilage ECM with anti-inflammatory activity, and a role in cell signalling.	Poor mechanical properties, and rapid degradation.
Alginate	Negatively charged polysaccharides extracted from brown algae and bacterial sources. High functionality, fast cross-linking, low cost, injectable for bioprinting, structural similarity to GAGs.	Poor mechanical strength, low cell-matrix interaction, varying levels of purity due to source variability, immunogenicity.
Agarose	A marine polysaccharide obtained from seaweed. It presents excellent biocompatibility, good stiffness and viscoelasticity. High functionality, thermoreversible gelation, low cost, structural similarity to GAGs.	Limited mechanical performance, low bioactivity, and poor cell attachment.
Chitosan	An amino polysaccharide polymer derived from chitin and the wastes of the seafood industry. Biocompatible and biodegradable. It possesses an antibacterial ability.	Poor water solubility in physiological conditions, potential allergenic risks, inferior mechanical properties, low cell adhesiveness, and potential allergenic reactions due to its origin.
Gellan gum	A linear negatively charged polysaccharide produced by the Sphingononas group bacteria; pH and temperature responsiveness, structural similarity to GAGs.	Weak mechanical strength, poor stability, low bioactivity, relatively high gelation temperature, small temperature window.
Collagen	The main protein component in natural cartilage displays great biocompatibility and biodegradation without causing inflammation.	Poor mechanical properties, potential of immunogenicity, high cost, limited serializability.
Gelatin	A derivative of collagen by partial hydrolysis with much lower antigenicity. Biologically active for cellular interaction, low immunogenicity in comparison to collagen, ease of processing and functionalization.	Poor mechanical properties, rapid degradation, low thermal stability,
Fibrin	Fibrin is a blood protein, well known for its role in clot formation, justifying its use in clinical practice as a hemostatic or a sealant agent. Hydrogels can be prepared from fibrinogen by the enzymatic treatment of thrombin; the advantages are excellent biocompatibility and biodegradability.	Weak mechanical properties.
Cellulose	One of many polymers found in nature may enter the composition of carboxymethyl cellulose, and in turn, hydrogel by specific processes.	Low integration. No degradability.

Preclinical research has also made use of hydrogels. To create a hydrogel that may be utilized as a microfracture adjunct, Gelrin (Regentis: Or-Akiva, Israel) utilizes fibrinogen polyethylene glycol, which is UV-activated in situ (Ahmed and Hincke, 2010). The first MACI product utilizing collagen membrane generated from pigs was recently authorized by the US FDA to treat knee cartilage problems. The following table shows the material of scaffolds.

Table 2: Materials of scaffolds

S.No.	Materials of scaffolds
1.	Hydrogels
2.	Collagen-based scaffolds
3.	EMC Scaffolds

6. Discussion

Recent advancements in medical research have paved the way for more comprehensive approaches that address both the symptoms and underlying causes of the disease. These approaches mentioned above aim to harness the body's natural healing mechanisms to slow disease progression and potentially reverse some of the damage caused by OA.Alongside these cutting-edge medical interventions, there is growing recognition of the crucial role that lifestyle modifications play in OA management. Personalized exercise programs, weight management strategies, and targeted nutritional therapies are increasingly being integrated into treatment plans. These non-pharmacological approaches not only help alleviate symptoms but also contribute to overall joint health and function.The holistic management of OA extends beyond conventional medical practices to include complementary therapies such as herbal medicine, acupuncture, and yoga. These alternative treatments offer additional avenues for pain relief and improved joint function, potentially reducing reliance on pharmacological interventions. Current research in OA continues to explore new avenues for treatment and management. Evaluation criteria for these emerging therapies are evolving, with a focus on not just symptom relief but also on slowing disease progression and improving long-term joint health. As our

understanding of OA pathophysiology deepens, so too does the potential for developing targeted interventions that address the root causes of the disease.

7. Conclusion

The management of osteoarthritis is evolving towards a more comprehensive and patient-centred approach. This shift represents a significant advancement in our understanding and treatment of this complex degenerative joint condition. By integrating innovative therapies such as regenerative medicine techniques with traditional treatments, lifestyle modifications, and complementary therapies, we are opening new avenues for more effective OA management.As research continues to advance our understanding of OA pathophysiology and mechanism of action, we can expect further refinements in treatment strategies. The ongoing development of novel therapies and the refinement of evaluation criteria will likely lead to more targeted and effective interventions. OA management offers hope for enhanced quality of life for millions of people worldwide affected by this condition. By combining the best of conventional medicine with cutting-edge treatments and lifestyle interventions, we are moving towards a future where OA can be managed more effectively, potentially slowing its progression and improving long-term joint health.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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