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Polymeric hydrogel-assisted chondro regenerative approaches towards cartilage injury therapy an emerging treatment option

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ABSTRACT

An injury to the cartilage is a physical disruption of the cartilage's architecture, resulting in fluid loss and pain to the individual. The earliest possible diagnosis of various cartilage defect complications is vital to facilitate healing. Moreover, to fasten the healing process of the cartilage defect, tissue-engineered materials should have several key characteristics, including ideal porosity, and minimal cytotoxicity. The primary characteristic of polymeric hydrogel scaffolds is that they offer a moist environment that accelerates the cartilage repair and good biocompatibility. Most often, biocompatible polymers and incorporated agents (such as stem cells, drug molecules, and bioactive agents) exhibit synergistic effects, resulting in very high therapeutic indexes. This review highlights the phases of cartilage repair, types of natural and synthetic Polymer loaded hydrogels used in Cartilage tissue regeneration, and the importance of the stem cells loaded hydrogel in cartilage tissue engineering concepts.

Keywords: Hydrogel, Cartilage defects, Tissue Engineering, Natural Polymers, Synthetic Polymers, Stem Cells.

INTRODUCTION

An injury to the cartilage is a physical disruption of the cartilage's architecture, resulting in fluid loss and pain to the individual. The earliest possible diagnosis of various cartilage defect complications is vital to facilitate healing [1]. Moreover, to fasten the healing process of the cartilage defect, tissue-engineered materials should have several key characteristics, including ideal porosity, high water retention potential, and minimal cytotoxicity [2].

Table 1: Represents the advantages and disadvantages of the polymers involved in the fabrication of the hydrogels for cartilage tissue regeneration.

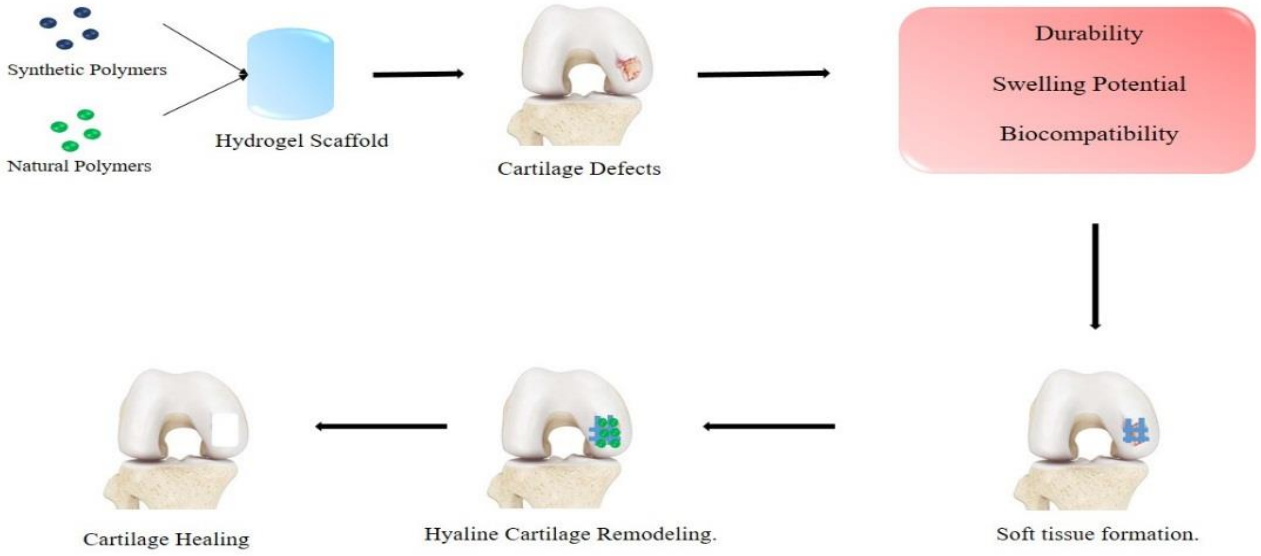
Name of the Polymer	Advantages	Disadvantages
Polyvinyl alcohol (PVA)	Shows ideal mechanical stability, and Biomimetic Characteristics [9].	Limited protein adsorption property of this polymer often results in low cell adhesion [11].
Polyethylene glycol (PEG)	The ability to modify while showing the variable mechanical characteristics, and efficiency in controlling scaffold structure, chemical characteristics and bioinert nature are some of the advantages PEG-based hydrogels [10].	Shown some limitations towards viability and the growth of the cells [12].
Chitosan	This polymer's hydrophilic characteristics and potential for enzymatic degradation by humans make it both biocompatible and biodegradable [5].	Chitosan-based hydrogels alone is typically ineffective for cartilage repair because of their minimal elasticity, and poor bio adhesive characteristics.
Alginate (Alg)	In contrast to aligning the mechanical properties of the scaffold with the natural tissue, the morphological attributes of the alginate hydrogel can be effectively tailored to mimic those of articular cartilage [6].	The lack of long-term durability in physiological settings of ionically cross-linked alginate gels is the major limitation for the alginate polymer.

Several limitations of surgical procedures (such as auto grafts) often cause the cartilage to not heal adequately due to their biodegradability and biocompatibility characteristics.

No existing product meets the entire set of requirements of the ideal dressing [3].

The following scenario leads to the development of novel hydrogel formulations to treat cartilage defects using natural and synthetic biocompatible polymers [4]. It is common to formulate hydrogel scaffolds from both natural and synthetic polymers (Figure 1 & Table 1).

Figure 1: Represents the importance of the Polymeric hydrogel scaffolds in the Cartilage Tissue Repair



However, the natural polymers in hydrogel scaffold fabrication include chitosan (CHI) and Alginate. Their non-cytotoxic, non-antigenic properties, biocompatibility, and biodegradable properties make them ideal polymers for cartilage repair [5,6]. Further, these natural polymers lack ideal mechanical properties compared to its counterpart (i.e., synthetic polymers) [7,8]. The synthetic polymers used in the formulation of the hydrogel scaffold for cartilage include poly vinyl alcohol (PVA), and poly ethylene glycol (PEG). Despite their excellent mechanical properties [9,10], these polymers have poor biodegradability [11,12]. This review highlights the phases of cartilage repair, various types of natural polymers and Synthetic Polymer loaded hydrogels used in Cartilage tissue regeneration, and the importance of the stem cells loaded hydrogel in cartilage tissue engineering concepts (Table 2).

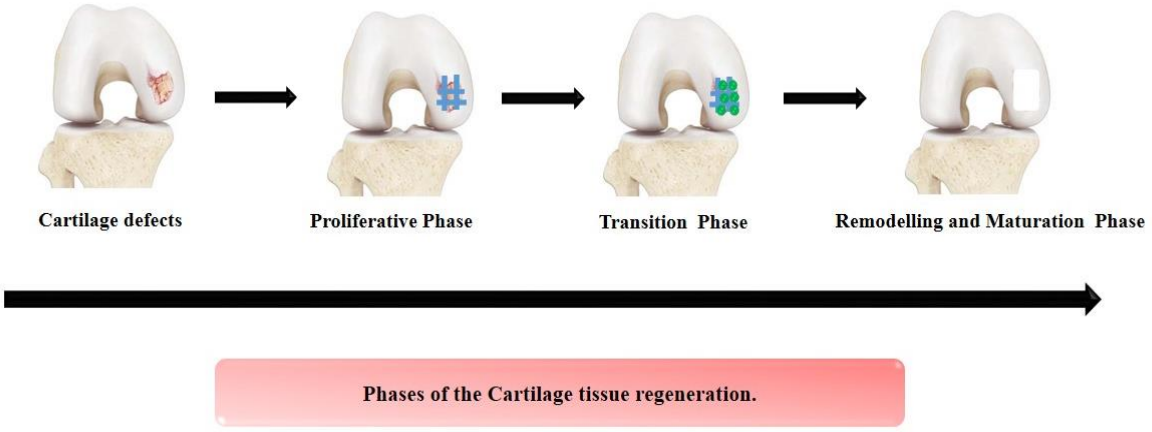
Table 2: Represents the significance of the polymeric hydrogel scaffolds in cartilage tissue regeneration.

Name of the formulation	Developed by	Significance
Chondrocyte extracellular vesicles and mesenchymal stem cells, entrapped in chitosan-hyaluronic acid hydrogel.	Heirani-Tabasi et al.	Treatment with EV / MSC loaded chitosan- hyaluronic acid hydrogel enhanced the SOX9 and COLII expression [18].
Bioinspired Functional Chitosan/Cellulose Nanofiber 3D Hydrogel	Kamdem Tamo et al.	The bioinspired CHI/CNF-filled hydrogels described here function via chitosan as a biocompatible and biodegradable matrix to support cell growth, and the CNFs intend to give the ideal mechanical characteristics for the hydrogels [19]
Chitosan/hyaluronic acid with silanized-hydroxypropyl methylcellulose	Hu et al.	Improved their swelling and rheological characteristics [20].
Metformin Hydrochloride Encapsulation by Alginate Strontium Hydrogel.	Xu et al.	Significantly inhibited the gene expressions related to, oxidation, and inflammation [23].
Alginate-poly (acrylamide) hydrogel with TGF-β3 loaded nanoparticles.	Saygili et al.	Shown minimal cytotoxic nature and excellent viscoelastic characteristics [24].
Ionically and Enzymatically Dual Cross-Linked Oxidized Alginate Gelatin Hydrogels.	Distler et al.	Appropriate hydrogel matrix for cell culture [25].
Gelatin-Silk Sericin Incorporated with file PVA Hydrogel-Based Nanocomposite.	Zhao et al.	Shown excellent cytocompatibility, and tissue regeneration potential [28].
Polyvinyl alcohol/type II collagen hydrogels.	Lan et al.	Demonstrated a high degradation ratio [29].
Fe_3O_4/ Polyvinyl alcohol (PVA)/type II collagen (COLII) magnetic nanocomposite hydrogel.	Huang et al.	Ideal porosity, swelling potential, and mechanical characteristics [30].
Silk Fiber Construct Embedded Dual-Layer PEG Hydrogel.	Kim et al.	Displayed the regulated degradability and offered a favorable environment for chondrogenesis [32].
Chondrocytes encapsulated PEG hydrogels.	Chu et al.	Triggering of free radical interaction often activates the antioxidant potential within chondrocytes by altering the properties of PEG hydrogels [33].
Well-dispersed platelet lysate entrapped nanoparticles incorporate with injectable PDLLA-PEG-PDLLA hydrogels.	Tang et al.	Ameliorates early cartilage degeneration and promotes cartilage repair [34].
Chitosan hydrogel/3D-printed poly (ε-caprolactone) hybrid scaffold containing synovial mesenchymal stem cells.	Li et al.	Enhanced cell proliferation and chondrogenesis [37].
WJ-MSC and BM-MSC incorporated Alginate (Alg) / Hyaluronic acid (HA) hydrogel scaffold.	Reppel et al.	Exhibit divergent chondrogenic development characteristics at the transcript and protein levels [38].
Chitosan/PVA hydrogel combined with Ad-hTGF-β1 transfected mesenchymal stem cells.	Qi et al.	Displayed the strong adhesion to the injured tissue, and lack of rejection [39].

Phases of Cartilage Repair

The biological process of cartilage repair is complex and dynamic, involving several phases, such as the inflammatory, proliferative, and maturation phases (Figure 2). In the inflammatory phase, the activation of the chondrocyte, neutrophils, and macrophages protects the cartilage defect site and prevents it from acquiring microbial infections, allowing it to heal faster [13]. The chondrocyte activation occurs immediately after the injury at the cartilage defect site. The duration of the inflammatory phase depends on the depth of cartilage injury [14].

Figure 2: Depicts the phases of the cartilage regeneration



Extracellular matrix (ECM), which includes hyluronic acid (HA), proteoglycans, and other components, forms connective tissue to replace the cartilage tissue defect. Cell proliferation, the development of thick connective tissue, and fibroblast cell differentiation at the defect site are the hallmarks of the proliferative phase. The proliferation phase involves several cytokines and growth factors, including the transforming growth factor β (TGF- β) and interleukin (IL) families. This phase usually lasts for 12 weeks [15]. The remodelling phase, also known as maturation, is the last stage of cartilage repair. During this phase, fully repaired and regenerated tissue at the cartilage defect contains a significant number of chondrocytes and glycosaminoglycan. This phase lasts for about 24 months [16].

Natural biocompatible polymers-based hydrogel scaffolds in cartilage tissue regeneration

Chitosan (CHI)

CHI, made of the amino acid glucosamine and acetylglucosamine, shares structural similarities with the glycosaminoglycans found in cartilage's ECM. Due to its advantageous structural characteristics and biodegradability, CHI and its derivatives have ensively been used in cartilage tissue engineering and regenerative medicine [17].

Extracellular vesicles (EVs) of cartilage cells have attracted much attention for their ability to differentiate into chondrogenic tissues, although cartilage regeneration has only recently become associated with them. Moreover, injectable hydrogels containing mesenchymal stem cells (MSCs) are employed to regenerate articular cartilage (AC) with varying clinical results. Heirani-Tabasi et al. treated the articular chondrocyte EVs generated from humans with chondrocyte EVs and cultured them in injectable chitosan-hyaluronic acid (CS-HA) hydrogel scaffolds. The in vivo studies and Magnetic resonance imaging (MRI) results demonstrated that the treatment with EV / MSC loaded CS-HA hydrogel promoted chondrogenic genes SOX 9, COLII expressions, and Col II protein expression and significant cartilage regeneration potential than the MSCs alone treatment group. Finally, the chondrogenic differentiation of MSCs, identified in osteoarthritis and cartilage injuries, could be promoted by chondrocyte-EVs and CS-HA hydrogel [18].

New strategies are possible to design environmentally friendly high mechanical performance composites based on the unique mechanical properties of native cellulose nanofibers. Kamdem Tamo et al. proposed the 3D print hydrogel constructs, composed of, respectively, CHI and cellulose nanofibers (CNF), that did not undergo any chemical modification or crosslink application prior to processing. In contrast to hard tissues, soft tissues are typically composed of fibers reinforced with hydrogel composites, characterized by a high water content and a low mineral content. Further, the bioinspired CHI/CNF-filled hydrogels described here function via CHI as a biocompatible and biodegradable matrix to support cell growth, and the CNFs intend to give the ideal mechanical characteristics for the hydrogels. Finally, the work offers new perspectives in the engineering of mechanically demanding hydrogel tissues, including intervertebral discs (IVDs), cartilage, and meniscus, among others, with CHI-based natural polymers [19].

Despite the threat of cartilage damage to humans, no successful treatment exists to restore its original function. Hu et al. developed a composite CS/HA and silanized-hydroxypropyl methylcellulose (Si-HPMC) hydrogel scaffold without adding any chemical crosslinking agents. According to the mechanical studies, incorporating the Si-HPMC into CS/HA hydrogels improved their

swelling and rheological characteristics but at the expense of compressive strength and an accelerated degradation rate. Hydrogels containing 3% (v/v) Si-HPMC and 2.5/4.0% (v/v) CS/HA are suitable for cartilage tissue engineering because of their physical and bioactive properties. Invitro studies have shown that the CS/HA/Si-HPMC hydrogels have increased cartilage proliferation and deposition. Additionally, after 21 days, CS/HA/ Si-HPMC (3%) hydrogels showed 79.5% regeneration potential, indicating the ideal in vivo cartilage regeneration. Finally, the biocompatible, biodegradable, and injectable scaffold containing CS, HA, and Si-HPMC is a promising candidate for cartilage tissue engineering concepts [20].

Alginate (Alg)

Alg is a biocompatible polymer with good porosity, high moisture content, and tunable viscosity. It is well known for its simplicity in forming hydrogels that can be used as scaffolds to hold cells and medications in the cartilage tissue engineering concepts [21,22].

The cartilage lesion is a common tissue defect that challenges clinical practitioners. The senescence of chondrocytes could impair cartilage tissue's ability to regenerate after trauma. Xu et al. developed an anti-inflammatory Alg hydrogel that combines metformin with strontium, a material that is effective for cartilage tissue engineering. An RT-PCR test determined that hydrogel significantly inhibited the expression of genes related to senescence, apoptosis, oxidation, and inflammation. Histopathological examinations showed that the metformin-incorporated alginate /strontium hydrogel significantly reduced chondrocyte senescence and fastened the cartilage repair. Finally, by inhibiting the senescence of cells and tissues, the metformin-incorporated alginate /strontium hydrogel treats cartilage defects and provides a new clue for accelerating tissue repair [23].

A lack of adequate clinical treatment for articular impairments has limited the function of current implantable materials. Saygili et al. developed a functionalized polyacrylamide-Alginate (PAAm-Alg) Double Network (DN) hydrogel that acts as an articular tissue. Over three months, these hydrogels remained mechanically stable at different temperatures (+4 °C, 25 °C, 40 °C) and humidity levels (60% and 75%). Further, the in vitro studies demonstrated the minimal cytotoxic nature and excellent viscoelastic characteristics of the PAAm-Alg hydrogel. Histological studies demonstrated that hydrogels significantly enhance cartilage regeneration in rats due to their stability and controlled TGF-β3 release. Finally, the results of this study demonstrated the potential of PAAm-Alg hydrogels for cartilage repair in humans [24].

In regenerative medicine, hydrogels are highly relevant because they allow the growth and maturation of tissue engineering constructs in vitro over an extended period. Among natural polysaccharide-based hydrogels, one of the best materials for long-term cell culture is versatile and chemically functionalized. Distler et al. developed the alginate dialdehyde / gelatin (ADA-GEL) hydrogel crosslinked via enzymatic (microbial transglutaminase, mTG) interaction, which can tailor the ADA stiffness and GEL hydrogels in a wide range of stiffness (from <5 to 120 kPa) without altering the chemistry of the hydrogels. On (+) mTG crosslinked ADA-GEL hydrogels, NIH3-T3 and ATDC-5 cells adhered and grew better than on new Ca2+ crosslinked gels. Therefore, ADA-GEL is an appropriate hydrogel matrix for cell culture, and this platform may be helpful when investigating the 3D printability of such hydrogels. The hydrogels demonstrate long-term stability, making them ideal for applications such as cartilage healing, where long incubation times are necessary for cellular maturity. Hence, mTG crosslinking appears to be a valuable way to overcome the fast degradation rate of high GEL-containing ADA-GELs for tissue engineering applications in the future [25].

Synthetic biocompatible polymers-based hydrogel scaffolds in cartilage tissue regeneration

Polyvinyl alcohol (PVA)

As a cartilage replacement material, PVA hydrogel has been successful because of its excellent components, high water content, low friction properties, and biocompatibility [26,27]. As an extracellular matrix, silk sericin and PVA have excellent potential in tissue engineering. Zhao et al. developed a novel GEL and silk sericin-polyvinyl alcohol (SS-PVA) hydrogel nanocomposite for accelerating the healing process in case of cartilage defects. GEL-SS-PVA scaffolds with higher PVA concentrations showed smaller pores and improved uniformity. In contrast, PVA increased the modulus and decreased the tensile strength of the membranes. Additionally, the in vitro and in vivo analyses showed that the hydrogels at the site of the cartilage tissue defect had excellent cytocompatibility, biocompatibility, biodegradability, and tissue regeneration potential. Finally, the silk sericin-loaded PVA/ gelatin hydrogel proved an ideal candidate for cartilage repair because of the excellent tissue regeneration potential [28].

The cartilage ECM comprises type II collagen (Col-II). Even though such natural materials are biocompatible, they cannot provide a supportive environment for seed cells to grow because of their poor mechanical strength. Lan et al. synthesized porous PVA/Col-II composite hydrogels for cartilage tissue engineering by incorporating different contents of Col-II into porous polyvinyl alcohol (PVA). Upon incorporation of Col-II, the composite hydrogels display an increase in elastic modulus for a short period (under moisture conditions) and then begin to decrease. Incorporating Col-II into the composite hydrogels demonstrated a high degradation ratio. Finally, PVA/Col-II hydrogels attained significant importance in tissue engineering or AC regeneration concepts [29].

To develop a clinical procedure for cartilage defect treatment, Huang et al. fabricated a new type of magnetic nano composite hydrogel based on Fe_3O_4, polyvinyl alcohol (PVA), and COLII. According to the study, the PVA/COLII, 95:5 hydrogel matrix was the best, while the Fe_3O_4/PVA/COLII, 5:95:5 magnetic nano composite hydrogel also displayed all-around good performance. However, taking these results together, the PVA/COLII, 95:5 matrix was determined to be the optimal hydrogel matrix because of its ideal porosity, cyto-compatibility swelling potential, and mechanical characteristics [30].

Polyethylene glycol (PEG)

Polymers such as PEG played a significant role in cartilage regeneration because of their ideal biological inertness, adjustable mechanical properties, and degradability characteristics. PEG hydrogels offer a three-dimensional environment that is sufficiently similar to native cartilaginous tissues for the maintenance and investigation of chondrogenic phenotype and chondrogenic differentiation [31].

In order to repair damaged cartilage, researchers are exploring ways to employ biomaterials such as hydrogels to regenerate the damaged cartilage. Hydrogel composites have the necessary mechanical properties to repair cartilage. Kim et al. developed a dual-layered composite hydrogel that mimics the layered structure of cartilage. PEG hydrogel with eight arms and PEG diacrylate prepared by thiol-norbornene photo-click chemistry forms the top layer of the implant. The top layer had a compressive modulus of 700.1 kPa. A 3D silk fiber construct reinforced with a low-density PEG hydrogel in the bottom layer displayed the regulated degradability and offered a favorable environment for chondrogenesis. Doing so increases the effectiveness of Composite Hydrogel meant for cartilage repair [32].

Hydrogels made from Photo polymerizable PEG are a promising technology for encapsulating and engineering cartilage tissue. Chu et al. demonstrated that chondrocytes disrupt hydrogel formation during encapsulation, reducing PEG hydrogels' bulk and local crosslink density. The activation of freshly isolated chondrocytes on hydrogel precursors was associated with thiol-mediated events between dithiol crosslinkers and free thiols on the cell surface, which led to a reduction in crosslink density in the bulk hydrogel. As cellular density increased at the time of encapsulation, this effect became more prominent. The chondrocytes can get embedded with a gradient in hydrogel density around them by pre-treating the cells with the antioxidant estradiol before encapsulation. As a result of these gradients, a hydrolytically degradable PEG hydrogel developed spatial variations in its degradation behaviour. These findings demonstrate that triggering free radical interaction often activates the antioxidant potential within chondrocytes by altering the properties of PEG hydrogels. Finally, interactions like these show promising effects in cartilage tissue engineering because of their effects on the growth and microenvironment of the cells within hydrogels [33].

In recent years the use of platelet lysate (PL) as a cost-effective cocktail of growth factors as a potential component of regenerative medicine enhanced rapidly, especially for cartilage replacement. The majority of studies, however, ignore the intrinsic characteristics of PL and incorporate them into scaffolds or hydrogels simply by mixing them. According to Tang et al., the direct introduction of PL into thermo sensitive poly (d,l-lactide) poly (ethylene glycol) poly (d,l-lactide) (PLEL) hydrogel disturbed its sol-gel transition. This method of incorporating PLNPs into PLEL gels demonstrated a long-term gelling capability and PL-releasing capability. The PLEL @ PL-NP system effectively ameliorates early cartilage degeneration and promotes cartilage repair in an in vivo setting. Additionally, the IL-1β-induced chondrocytes did not dedifferentiate or undergo inflammation in response to the PL-loaded composite hydrogels. In sum, these data suggest that well-dispersed PL from Hep/EPL NPs efficiently incorporates into hydrogels, and the constructed system, PLEL@PL-NPs, can be used to engineer cartilage tissue stepwise [34].

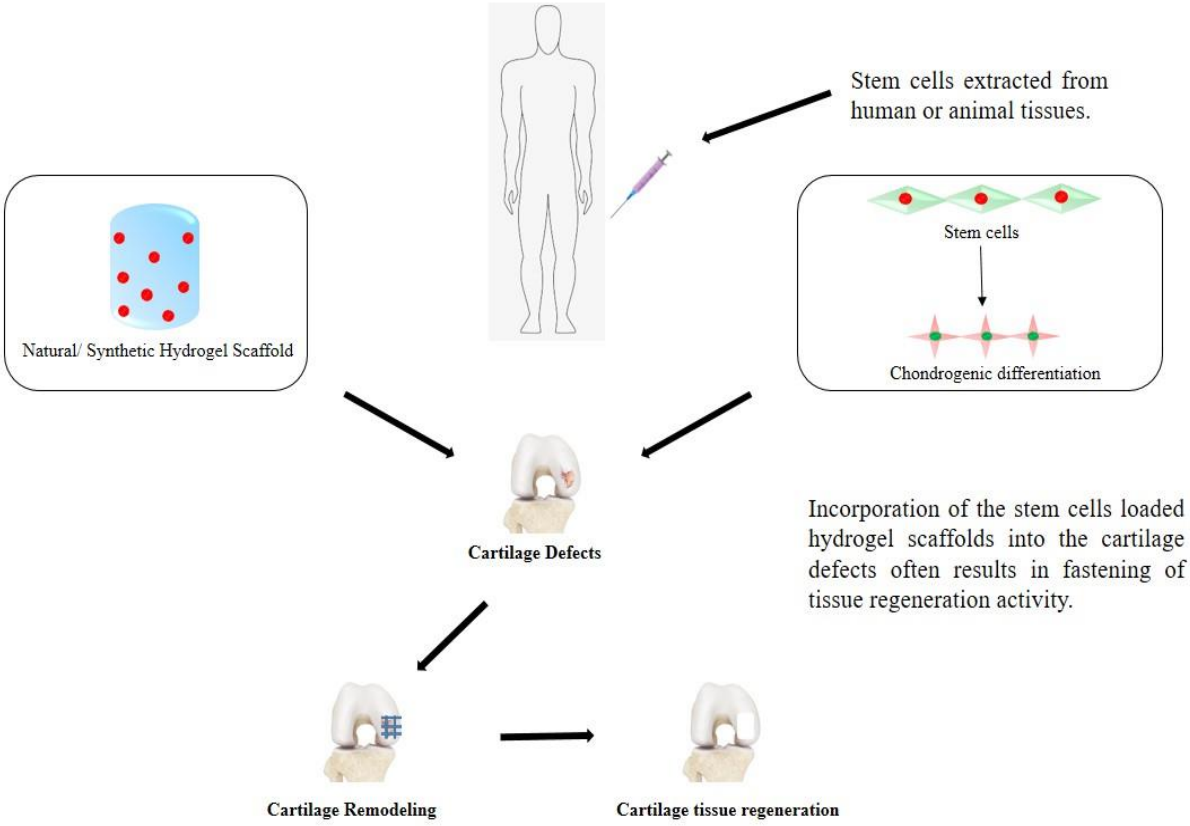
Importance of the stem cells loaded hydrogel scaffolds in cartilage tissue engineering concepts

Due to its ideal biocompatible, biodegradable, cellular proliferation, and differentiation characteristics, stem cell-loaded hydrogels have recently experienced tremendous growth. The most alluring feature of these stem cell-loaded hydrogels is their high tissue specificity (Biomimetic Property), which results in highly effective cartilage healing. This high tissue specificity is confirmed by promoting chondrogenesis or osteogenesis (Figure 3) [35,36].

Restoring AC injuries has long been a challenge for the formulators. Recently, mesenchymal stem cells (MSCs) have demonstrated the ability to regenerate cartilage. Synovial mesenchymal stem cells (SMSCs) are endogenous articular stem cells with significant chondrogenic differentiation potential and articular localization. Li et al. developed a chitosan hydrogel/3D-printed poly caprolactone (PCL) hybrid containing SMSCs and tetrahedral framework nucleic acid (TFNA) and injected it into the articular cavity for facilitating DNA cartilage regeneration. TFNA, a promising deoxyribonucleic acid (DNA) nanomaterial for enhancing the regenerative milieu, could be absorbed into SMSCs, encouraging their growth and differentiation into chondrogenic cells. After being injected into an articular cavity in vivo, CS, a cationic polysaccharide, can bind to DNA via electrostatic interaction and attract free TFNA. The 3D-printed PCL scaffold supplied essential mechanical support, while TFNA enhanced cartilage regeneration and created a favorable microenvironment for the proliferation and chondrogenic differentiation of the delivered SMSCs, considerably fastening the

tissue regeneration at the injured site of the cartilage. Finally, these findings support the notion that a CS hydrogel/3D-printed PCL hybrid scaffold, including SMSCs, may represent a potential approach for cartilage regeneration predicated on pc-directed TFNA recruitment and TFNA-enhanced cell proliferation and chondrogenesis [37].

Figure 3: Importance of the stem cells loaded hydrogel scaffold in the cartilage regeneration.



Although considerable research has successfully induced chondrogenesis in Wharton's jelly - Mesenchymal stem cells (WJ-MSC) in 3D scaffolds, Reppel et al. demonstrated that chondrogenic differentiation of WJ-MSC can occur without incorporating the growth factors. WJ-MSC and Bone marrow- Mesenchymal stem cells (BM-MSC) exhibit divergent chondrogenic development characteristics at the transcript and protein levels if seeded on the CS-HA hydrogel scaffold. WJ-MSC placed in a 3D environment could adapt after four weeks and express particular genes and matrix proteins relevant to cartilage. Due to their ability to develop into cartilage, minimal immunogenicity, and ease of obtaining, WJ-MSCs are a great alternative source of stem cells for cartilage tissue engineering. Applying mechanical stress, hypoxic culture, and turning to stratified cartilage tissue engineering would be fascinating ways to improve the physiological environment imitating and enhancing chondrogenic differentiation. This novel spraying technique can create stratified engineered tissues by spraying successive layers of cells and hydrogels. Finally, the WJ-MSC embedded in Alg/HA hydrogel must be explored further in preclinical and clinical in vivo experiments [38].

Qi et al. demonstrated the therapeutic potential of thermo sensitive chitosan/polyvinyl alcohol composite hydrogel-engineered Ad-hTGF-β1-transfected bone marrow mesenchymal stem cells in the treatment of rabbit AC lesions. This study offers early evidence that CS/PVA gel can be used as an injectable material in tissue engineering to repair AC defects, and the regenerated cartilage can secrete cartilage matrix and carry out hyaline cartilage functions. The use of this gel for cartilage regeneration has benefits, including the need for only a modest surgical operation, strong adhesion to the injured tissue, and lack of rejection. Real-time polymer chain reaction (RT-PCR) and Western blot validated the activation of the hTGF-β1 gene in BMSCs. After transfection with Ad-hTGF-β1, BMSCs began to produce specific cartilage differentiation markers such as aggrecan micro ribonucleic acid (mRNA) and Collagen II. However, knee adhesion also happened in a few experimental animals, indicating that further investigation is needed to ascertain the long-term biomechanical stability of the regenerated cartilage tissue, as well as whether the newly formed cartilage cells are likely to experience dedifferentiation [39].

CONCLUSION

The primary characteristic of polymeric hydrogel scaffolds is that they offer a moist environment and good biocompatibility for accelerating the cartilage repair process. The findings of this manuscript demonstrate that both natural and synthetic polymers are a versatile group of polymers for developing biocompatible hydrogels to

treat cartilage defects. Most often, biocompatible polymers and incorporated agents (such as stem cells, drug molecules, and bioactive agents) exhibit synergistic effects, resulting in very high therapeutic indexes. However, in the near future, these polymeric hydrogel scaffolds could be used as adjuvant therapies in combination with more traditional treatment (i.e., surgical approach) to treat the cartilage defect in the first instance.

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Conflict of interest

The authors declare that they have no conflict of interest.

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