Applications of Hydrogels in Osteoarthritis

Subjects: Orthopedics

Contributor: Zhanqi Wei, Tianhao Zhao, Wei Zhu, Xisheng Weng

Osteoarthritis (OA) is a common degenerative joint disease that causes disability if left untreated. The treatment of OA currently requires a proper delivery system that avoids the loss of therapeutic ingredients. Hydrogels are widely used in tissue engineering as a platform for carrying drugs and stem cells, and the anatomical environment of the limited joint cavity is suitable for hydrogel therapy. Hydrogel delivery improves drug retention in the joint cavity, making it possible to deliver some drugs that are not suitable for traditional injection; hydrogels with characteristics similar to those of the extracellular matrix facilitate cell loading, proliferation, and migration; hydrogels can promote bone regeneration, depending on their own biochemical properties or on loaded proregenerative factors.

Keywords: Osteoarthritis (OA) ; Hydrogels ; drug delivery system

1. Hydrogels as a Biomaterial

Hydrogels with different three-dimensional structures, porosities, elasticities, and mechanical strengths can be produced by selecting different molecular monomer reagents and crosslinking them in a physical or chemical manner in aqueous solution to form insoluble network structures [1]. As biological materials, hydrogels maintain a high moisture content through a crosslinked network with complex physical and chemical properties, which can be used to build a microenvironment similar to that of the extracellular matrix and suitable for cell survival [2].

According to the source of the monomer, hydrogels are mainly divided into two categories: naturally forming hydrogels (hyaluronic acid (HA), collagen, fibrin (FB), alginate, etc.) and synthetic hydrogels (e.g., polyethylene glycol (PEG)-based hydrogels) [3]. Hyaluronic acid is suitable as a drug carrier due to its bio-viscoelasticity, biodegradability, non-immunogenicity, and biomedical benefits [4]. Collagen hydrogels have excellent biocompatibility, but their use is limited by their weak mechanical properties. A study tried to introduce cellulose nanofibers to collagen hydrogels to modulate their physical properties [5]. Regarding alginate hydrogels, some studies altered their molecular weight and introduced backbone chemical modifications and covalent crosslinking to improve their degradability, mechanical properties, and cell adhesion, so to adapt them for special applications of tissue engineering [6]. For example, oxidized alginate-based hydrogels have improved degradability and reactive groups [7]. PEG-based hydrogels are used after crosslinking [8] or modification (with the –SH group) [9] as simple scaffolds, and afford fast and gentle coagulation and excellent drug dispersion, respectively. Interestingly, synthetic hydrogels based on PEG were used as biomaterial earlier than natural hydrogels, probably due to the rapid development and maturation of polymeric technology and materials in the industry [10]. HA-based natural hydrogels have long been used as soft-tissue fillers or for viscosupplementation in the synovial cavity of patients, which are very different applications from those in the biomaterials field discussed herein [11]. Natural hydrogels were later gradually studied as biomaterials rather than drugs because of their excellent biocompatibility and degradability [12].

Hydrogels are now widely used to promote angiogenesis [13], tissue regeneration in the central nervous system [14], and cartilage generation in plastic surgery [15]. Both vascular tissue and cartilage need to bear stress and maintain elasticity, which are properties of hydrogels. In addition, porous hydrogels can be loaded with materials as small as drugs and as large as cells to serve a variety of functions for tissue regeneration. These features are also useful for Osteoarthritis (OA) treatment.

2. Therapeutic Effects of Hydrogels

Regardless of other functions, hydrogels, especially HA-based ones, have a therapeutic effect on OA by themselves. Intra-articular injections of HA and chondroitin sulfate replenish joint fluid and reduce friction between joint cartilage surfaces to relieve pain [16]. A recent retrospective study concluded that intra-articular injections of HA in patients with mild and severe hip OA might relieve pain and improve function. Furthermore, three consecutive injections resulted in a better analgesic effect, which is the main effect of HA [17].

It should be noted that the efficacy of HA is limited. One analysis found that while both corticosteroids and HA reduced the risk of surgery for patients within 10 years, the risk of surgery and the cost of treatment were slightly higher in the HA cohort than in the corticosteroid cohort [18]. Another clinical trial found that corticosteroids and HA were able to alleviate OA progression, but patients treated with HA injections were at a higher risk of total knee replacement [19]. The possible combination of HA with other drugs is a more appropriate clinical approach. The results of a double-blind randomized experiment showed that long-term combined injections of HA and corticosteroids were more effective at relieving joint pain and improving motor function and physical condition than injections of HA alone [20]. Clinically, a Russian study recommends oral NSAIDs for patients with persistent symptoms of OA, supplemented by intra-articular HA and corticosteroids, especially if other drugs do not elicit a response [21].

In addition, hydrogels of nonmammalian origin, such as hydrogels based on chitosan and alginate, are also being examined for their therapeutic significance, as their thixotropy, nontoxicity, and drug release capability suggest their potential for viscosupplementation [22][23][24].

3. Hydrogel Implantation in Joints

As mentioned earlier, both monomeric (non-crosslinked) and polymeric (crosslinked) forms of HA have been accepted for the treatment of pain associated with knee OA [25]. It was later discovered that hydrogels with porous structures are able to release drugs slowly into the synovial cavity, promoting cell proliferation and tissue formation and thereby inhibiting inflammation and repairing cartilage [26]; these hydrogels could thus be used to develop sustained-release systems [12]. A cyclodextrin pseudopolyrotaxane system mixed with attapulgite was used to form a supramolecular hydrogel with a composite structure similar to that of “reinforced concrete”, allowing the sustained release and subsequent anti-inflammatory effects of diclofenac sodium [27]. Furthermore, the hydrogel backbone can also carry cells and deliver physicochemical signals and nutrients for cell growth [26][28].

Biocompatibility, biofunctionality, mechanical properties, and adjustable degradation of polymer hydrogels are basic characteristics of hydrogels used intra-articularly [29]. Naturally forming hydrogels have outstanding biocompatibility, low immunogenicity, low cytotoxicity, and an excellent capability to promote cell adhesion and proliferation and new tissue regeneration compared to synthetic hydrogels [29][30]. However, natural hydrogels are degraded via diverse pathways in vivo, which reduces their efficiency. Physiologically, HA is degraded by intracellular and serum enzymes or decomposed by heat and oxidants [25]. FB is rapidly broken down by plasmin. By adding fibrinolytic inhibitors [31] or inducing polymerization with synthetic hydrogel monomers such as PEG [32], the degradation rate of natural hydrogels can be tuned, and their stability can be improved. The variety of natural hydrogels is limited; thus, natural hydrogels sometimes cannot meet applications’ needs. Synthetic hydrogels are of interest for achieving longer efficacy, a higher gel strength, and customizable functionality and degradability, although their poor compatibility still has to be overcome [33]. Some researchers have tried to develop composite hydrogels using complementary natural and synthetic sources, such as a double-network hydrogel of poloxamer–heparin/gellan gum [34] and a hydrogel platform based on PEG and gelatin [35]. The poloxamer–heparin/gellan gum hydrogel formed a microenvironment conducive to stem cell growth, and in vivo experiments showed that it supports bone marrow stem cell survival, attachment, and extracellular matrix production. The PEG/gelatin hydrogel could effectively promote cell differentiation, with an effect better than that of the heterogeneous protein mixture Matrigel and exhibited improved strength due to the covalent binding of PEG.

4. Hydrogel-Based Intra-Articular Drug Delivery

As mentioned earlier, the intra-articular injection of HA polymers into patients with OA can relieve pain. It is known that small-molecule NSAIDs often undergo rapid depletion. Experiments have shown that some drugs (paracetamol) and proteins (albumin) are not retained long enough in the joint cavity and may not be suitable for injection therapy in free form [36]. Therefore, some kind of matrix is needed to carry drugs and release them locally in a sustained manner so to achieve a long-term treatment. Hydrogels can maintain high local concentrations of drugs for a long time. Abundant crosslinking and expansion upon water absorption allow hydrogels to form a loose and porous microenvironment, which can be loaded with a variety of drugs. The ratio of feedstock or synthesis can be changed to adjust the size and density of the voids and adapt hydrogels to the molecular size of drugs and to the required rate of drug diffusion [37]. A biodegradable ternary hydrogel from oxidized dextran (Dex-ox), gelatin, and HA was injected to deliver two different anti-inflammatory drugs, i.e., naproxen (NSAID) and dexamethasone (Dex). New Zealand rabbits in the experimental group presented a low macroscopic degree of OA in the injected knees and better recovery [38]. Tyramine-modified HA (HA-Tyr) hydrogels encapsulating Dex resulted in the successful treatment of rheumatoid arthritis (RA) [39]. Although RA and OA are not the same disease, HA-Tyr hydrogels still provide ideas for intra-articular corticosteroid delivery. Good therapeutic effects were also achieved by the delivery of anti-inflammatory drugs such as indomethacin and celecoxib using a hydrogel system in

animal experiments [40][41][42]. Through the use of combinations of hydrogels and other biomaterials, it is possible to prolong the sustained release of drugs and improve the performance of hydrogels. An injectable carboxymethyl chitosan–methylcellulose–pluronic hydrogel encapsulating meloxicam-loaded nanoparticles showed a reduced rate of gel degradation. Meloxicam was released separately from the gel and the nanoparticles, which extended the delivery time relative to the use of the hydrogel alone [43].

Hydrogels have also been used in an attempt to sustain the concentration and functioning of some drugs that are unstable in solution, such as kartogenin (KGN), in the joint [44]. KGN stimulates the differentiation of multipotent mesenchymal stem cells (MSCs) and the subsequent repair of damaged cartilage. A carrier system based on halloysite nanotubes and a laponite hydrogel demonstrated the slow release of KGN over 7 days [45], while another PEG-HA hydrogel reduced the release rate of KGN via covalent integration [46]. Cordycepin has been shown to inhibit the expression of ADAMTS-5 and MMP13 in IL-1β-induced OA, thus preventing inflammation. A hyaluronic acid methacrylate (HAMA) hydrogel together with chitosan microspheres could support the long-term release of cordycepin in a controlled manner [47]. Another ADAMTS-5 inhibitor (114810), with an HA hydrogel as a carrier, promoted cartilage healing in an osteochondral defect model [48]. Furthermore, cordycepin protected chondrocytes by facilitating autophagy. Several autophagy activators, including sinomenium and rapamycin, can also be delivered to ameliorate cartilage matrix degradation [49][50].

In addition to small-molecule drugs, some protein drugs, nucleic acids, and tissue extracts can be delivered using modified hydrogels. The affinity of HA itself for proteins is not sufficiently high. Sulfated HA showed not only improved protein sequestration but also greater resistance to hyaluronidase-induced decomposition, allowing the long-term action of the protein-hydrogel delivery system [51]. Platelet-rich plasma (PRP) promotes cartilage matrix synthesis and cartilage repair because it contains growth factors. However, the injected dose of PRP is easily lost from the synovial cavity, and the effect is very fast and unsustainable [52]. Gelatin (GLT) hydrogel microspheres loaded with PRP achieved increased expression of proteoglycan core protein mRNA in articular cartilage [53], while a genipin (GP)-HA/fucoidan (FD)/gelatin system facilitated the sustained release of PRP growth factors [54]. Exosomes are widely present in body fluids, are filled with proteins and RNA [55], can be used to encapsulate drugs, and can be delivered by hydrogels. Some researchers incorporated PRP-derived exosomes in an hydrogel matrix consisting of an optimal mixture of poloxamer-407 and poloxamer-188, significantly increasing the lifespan and retention of exosomes in joints and thus the duration of PRP release, which lasted continuously for 28 days, showing therapeutic effects [56].

Some responsive hydrogels are used to ensure that drugs can be evenly and stably dispersed before implantation, ensuring sustained release; the most common of these are temperature-responsive hydrogels. As an inexpensive synthetic corticosteroid, Dex is often used in the development of temperature-responsive hydrogels. The Dex-loaded thermosensitive hydrogel developed by Qi-Shan Wang et al. coagulated at 37 °C, and the cumulative release curve after coagulation showed that Dex was released slowly over 7 days, resulting in an analgesic effect and inflammatory factors downregulation in mouse OA models [57]. The formation of the thermal response of another N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-based Dex prodrug was accidental, and the researchers attributed this effect to the high level of Dex precursor in the polymer solutions. This precursor drug solution gelled in the joint or at temperatures above 30 °C and was retained for 1 month, during which the released precursor drug could be processed by phagocytes to produce free Dex, improving symptoms of OA [58]. A celecoxib-loaded hydrogel based on a fully acetyl-capped ε-caprolactone-co-lactide (PCLA)–PEG–PCLA triblock copolymer transitioned to a gel at 37 °C and showed sustained celecoxib release for 90 days after a 10-day lag period [40]. Glucosamine (GlcN)-loaded thermosensitive hydrogels based on poloxamer-407 and poloxamer-188 slowly released GlcN in vitro and decreased the degree of swelling and the levels of inflammatory factors after intra-articular administration to treat OA in rabbits [59]. Temperature-responsive hydrogels also exhibit the therapeutic effects of the hydrogels themselves.

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