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Hydrogels for Induction of Bone Tissue Regeneration

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Abstract Bone tissue regeneration is an important aspect of medical practice, necessary for the treatment of injuries, osteoporosis and other bone pathologies. In recent decades, there has been an increase in interest for employing hydrogels as promising materials for stimulating bone tissue regeneration. Hydrogels are three-dimensional structures that can hold large amounts of water and create a soft environment similar to human tissue. These materials can be functionalized to provide suitable stiffness, structure, and bioactive molecules such as growth factors and cells. This article discusses various strategies for using hydrogels in inducing bone regeneration, including their role in delivering bioactive molecules and supporting cell adhesion and proliferation. The focus is on the development of hydrogels capable of reconstructing bone morphology and function, and the advantages and limitations of such approaches are discussed.

Keywords Hydrogels, Bone tissue regeneration, Regeneration induction, Biomaterials, Osteogenesis, Growth factors, Bone defects, Bone implants

1. Introduction

Restoring bone tissue is an urgent task in modern medicine, since damage or loss of bones can significantly limit functionality of the body and affect the patient's quality of life [15].

Extensive bone defects can be the result of trauma or surgery. Trauma can cause significant damage to bones, requiring intervention to restore structure and function. Surgical procedures associated with the removal of malignant tumors or areas of bone affected by osteomyelitis can also lead to extensive defects of the bone organ. Such defects are significant and may require specialized techniques and materials for recovering. The extent of these defects may vary. When developing suitable regenerative technologies, their characteristics must be taken into account. Filling a bone tissue defect in such cases is a complex task, requiring innovative approaches and the use of modern technologies. However, thanks to the development of scientific and medical advances, new methods and materials are emerging for the restoration of bone tissue defects. The use of hydrogels, bone grafting, the use of biocompatible materials and regenerative medicine techniques provide promising opportunities for the effective restoration of large bone defects.

Thus, extensive bone defects can be caused by various reasons, such as trauma or surgery. However, thanks to modern technologies and methods of regenerative medicine, there is hope for successful restoration and regeneration of bone tissue in such defects [32].

Currently, there are several methods for inducing bone regeneration, such as auto transplantation, all transplantation and the use of synthetic implants [5,7]. However, these methods are not without drawbacks, such as limited availability of donor material, risk of rejection, and difficulty in creating structures that match the patient's anatomical features [8].

Understanding the role of hydrogels in bone regeneration is essential for the further development of effective bone repair strategies. Research in this area may lead to the development of new approaches and materials that can improve the efficiency and reliability of bone grafting techniques.

In recent years, hydrogels have gained wide acceptance in the osteological field of regenerative medicine [35,45]. Hydrogels are three-dimensional polymer networks that can hold large amounts of water and have a number of unique properties that make them useful for clinical applications. Water is the main component of hydrogels, accounting for more than 90% of their mass in the swollen state. When hydrogels are used in contact with body tissues and cell cultures, water not only serves the function of providing a moist environment, but also controls the penetration of nutrients into cells [4,53,65].

Hydrogels can be divided into two main categories depending on the nature of the polymer components included

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in their composition. The first category is natural hydrogels, which include chitosan, alginate, hyaluronic acid, fibrin and collagen. The second category is synthetic hydrogels, which include polyethylene glycol (PEG), polyvinyl alcohol (PVA), polypropylene fumarate (PPF) and polyhydroxyethyl methacrylate (PHEMA) [21].

Hydrogels made from natural and synthetic polymers are various materials with unique properties and a special chemical structure. Natural hydrogels are typically derived from biological sources such as seaweed or animal tissue and are biocompatible and biodegradable. On the other hand, synthetic hydrogels are created through chemical synthesis and have strictly controlled properties such as mechanical strength and degradation parameters.

The classification of hydrogels into natural and synthetic variants is based on the chemical composition of the polymers used and is an important aspect in their further application and customization for specific medical or biological applications [21].

Hydrogels are typically created by polymerizing monomers in the presence of a cross-linking agent or through chemical reactions that result in the formation of a three-dimensional network of polymers [34]. These polymers can be of either natural or synthetic origin. Some of the most common polymers used in hydrogels include polyacrylamide, polyvinyl alcohol, polyethylene glycol, alginates and hyaluronates [13]. Hydrogels are used in the regeneration of various tissue types, including skin, muscle, bone, nerves and blood vessels [66].

The properties of hydrogels, such as water absorption, hydrophilicity and porous structure, make them ideal for use in regenerative medicine [43,67]. Hydrogels can retain and transport nutrients and bioactive molecules, as well as provide mechanical support and tissue protection [24,35]. They also have biocompatibility, which allows them to interact with cells and tissues without causing negative reactions from the body [38,66].

Due to their properties, hydrogels are widely researched and used in various medical fields, including regenerative medicine, tissue engineering, drug delivery, and implantation of bioactive substances. In the context of bone regeneration, hydrogels are a potentially important tool for the creation and delivery of biocompatible materials capable of supporting the restoration of damaged or lost bone tissue [1,2].

2. Materials and Methods

The structure of hydrogels is determined by a three-dimensional network of polymer chains that are interconnected by cross-links. This network has a porous structure that can absorb and retain water or other liquids within its interior. Hydrogel pores can be of different sizes and shapes, which affects its properties and functionality [10,42,55].

The formation mechanisms of hydrogels may vary depending on the type of polymer and synthesis method. One of the common methods for their creation is the polymerization of monomers in the presence of a cross-linking agent. This can occur using chemical reactions involving the formation of covalent bonds between polymer chains. Another method is the physical binding of polymers, for example, through the interaction between polymer chains using hydrogen bonds [31,47,51].

One common example of a mechanism for the formation of hydrogels is the cross-linking of polymer chains through radical polymerization. In this case, monomers with functional groups capable of forming covalent bonds undergo polymerization under the influence of an initiator that generates free radicals. Radicals form bonds between monomer units, forming a three-dimensional polymer network [18].

Another method for the formation of hydrogels is the use of cross-linking agents. In this case, polymer chains with functional groups react with a cross-linking agent, forming covalent bonds and creating a three-dimensional hydrogel structure. Cross-linking agents can be added during polymerization or reaction with pre-existing polymer chains [34,39].

In addition, there are methods for forming hydrogels without the use of chemical reactions, such as thermal bonding or self-assembly, which rely on physical interactions between polymers, such as hydrophobic interactions or hydrogen bonds [9,40,64].

All these methods for the formation of hydrogels make it possible to create materials with different properties: different mechanical strength, water absorption, porosity and degradability. This makes hydrogels versatile materials in the field of regenerative medicine and tissue engineering.

Hydrogels have a number of key properties that make them promising for use in bone tissue regeneration. One of these properties is high water absorption capacity, which creates a moist environment that promotes biological processes: cellular activity, migration and differentiation.

This is particularly important for bone regeneration as it facilitates the diffusion of nutrients and regenerative growth factors necessary for efficient bone regeneration [50]. The hydrophilicity of hydrogels also allows them to mimic the natural extracellular matrix, creating a three-dimensional environment for cell growth and tissue regeneration [12].

Smart hydrogels are polymeric materials that have the ability to interact with the environment and changes in it in order to regulate their physicochemical properties. They are able to absorb water and form gels with high water-holding capacity. However, the key feature of smart materials is their ability to respond to various stimuli, such as changes in temperature, pH level, ion concentration, etc. This reactivity makes it possible to control the release of substances from hydrogels, which has applications in biomedical and pharmaceutical fields [35,37]. In addition, hydrogels can have a porous structure that allows the diffusion of nutrients and regenerative growth factors necessary for effective bone regeneration [2]. The composition of hydrogels can be chemically similar to natural bone tissue, which promotes their integration with surrounding tissues and maintains mechanical stability [3]. The tissue-mimicking properties of hydrogels allow them to integrate with surrounding tissues, maintain mechanical stability, and provide optimal conditions for cellular activity and bone formation.

Hydrogels serve as carriers for the delivery of regenerative growth factors such as peptides, proteins and genetic constructs that can induce proliferation, differentiation and bone formation. They can control the release of growth factors over time, providing sustained and long-lasting delivery of repair signals to the site of bone damage [54,57]. There are several methods for introducing growth factors into hydrogels to achieve bone tissue regeneration. One such method is dual growth factor sequential release, where a hydrogel scaffold system is used to sequentially release two growth factors to maximize bone regeneration [26]. Nanocomposite hydrogels are another approach that can mimic the natural extracellular matrix and stimulate cell adhesion and proliferation without the use of growth factors [41,57]. Biopolymers such as collagen and hyaluronic acid can mimic hydrogels to improve existing bone tissue engineering methods [59]. Biodegradable polymer hydrogels, including polyethylene glycol (PEG) and polyvinyl alcohol (PVA), can also be used for bone regeneration [14].

Additionally, growth factors such as bone morphogenetic proteins (BMPs) can be incorporated into hydrogels to accelerate the bone regeneration process [28]. In addition to the use of hydrogels containing BMP-2, there are various types of hydrogels that are of potential interest for the treatment of bone defects. Some of these types include hybrid implants where hydrogels are combined with bioceramic particles containing recombinant BMP-2 proteins and lysostaphin to treat bone defects [25]. Another approach is the use of gene-activated hydrogels, which allow the delivery of gene constructs to induce bone tissue regeneration [6].

To improve the regeneration of soft tissues, decellularized adipose tissue is widely used as a conductor. However, recent research suggests that adipose tissue may also be useful in promoting wound healing due to its favorable physical characteristics and biological properties. In this study, the researchers created a hydrogel using decellularized adipose tissue and another hydrogel containing vascular endothelial growth factor (VEGF) and heparin (called VEGF hydrogel). The results showed that the release of VEGF from the hydrogel lasted up to 3 days and also promoted collagen deposition and new blood vessel formation to a greater extent than other treatment groups. Researchers concluded that VEGF hydrogel has great potential as a biomaterial for various clinical applications [30].

Bone morphogenetic protein-9 (BMP-9) is known to be most effective in inducing bone formation. In the studies, the researchers used a multicomponent scaffold gel combining BMP-9 and vascular endothelial growth factor (VEGF) to study their ability to form bone. The gel consisted of chitosan microparticles (MPs) as carriers of BMP-9 and a thermosensitive gel loaded with VEGF. Gelation occurred at physiological temperature, which facilitated the injection and concentration of factors in the target area. Over a two-week period, the gel showed higher release of VEGF than BMP-9.

3. Results and Discussions

Human mesenchymal stem cells (hMSCs) embedded in the gel maintained their viability and showed enhanced proliferation and osteogenic differentiation when administered BMP-9. In vivo experiments showed that the BMP-9-VEGF combination gel significantly enhanced bone formation both subcutaneously and orthotopically during cranial bone injury. These results indicate the potential of MPS gel containing BMP-9-VEGF as an injectable engineering platform in bone tissue formation [17].

Various methods have been used to evaluate the efficiency of delivery of gene constructs using gene-activated hydrogels. One approach involves quantifying DNA release from hydrogels, which allows the efficiency of gene delivery to be assessed [44]. Changing the physical properties of the hydrogel carrier, such as the pore size of the gel, to achieve control over the delivery of genetic constructs [48]. For stem cell transplantation, hydrogels can be used in non-integrative approaches that isolate cells from recipient tissues [61]. Nonspecific interactions, such as direct physical encapsulation or electrostatic immobilization, can be used for localized delivery of viral genes [56]. Another gene delivery strategy targeting metastatic tumors involves the use of hydrogels capable of secreting specific matrix metalloproteinases [63].

In general, the use of methods for measuring DNA release, changes in the physical properties of the hydrogel carrier, non-integrating approaches, non-specific interactions and the secretion of specific matrix metalloproteinases allows us to quantify the efficiency of delivering gene constructs using gene-activated hydrogels.

Researchers have used a variety of strategies to ensure the stability and activity of growth factors in hydrogels, including encapsulation, covalent binding, physical adsorption, and combination with other materials. Encapsulation is the process of enclosing growth factors within a hydrogel, which protects them from degradation and maintains their activity. When encapsulated, growth factors are placed inside a hydrogel, which allows you to create a protective shell around them. This helps prevent their breakdown or degradation caused by environmental factors such as enzymes or physical stress. The protective shell of the hydrogel prevents unwanted changes in the structure and function of growth factors, maintaining their activity. When hydrogels are used for tissue regeneration, encapsulated growth factors can be released in a controlled manner as needed to stimulate the tissue regeneration process [11]. Covalent binding allows growth factors to be tightly bound to the hydrogel, preventing their diffusion and maintaining activity [49]. Physical adsorption is a process by which growth factors can be physically absorbed or bound to the surface of a hydrogel. Hydrogel, in this case, is a material with special properties that facilitate interaction with growth factors. When growth factors are physically adsorbed onto the surface of the hydrogel, they remain on it and retain their activity. The process of physical adsorption ensures not only the retention of growth factors on the surface of the hydrogel, but also prevents their diffusion or loss of activity. Physical adsorption is one of the methods used to ensure the stability and activity of growth factors in hydrogels. It allows growth factors to be closely associated with the hydrogel, maintaining their biological activity and ability to stimulate bone tissue regeneration [20]. Additionally, growth factors can be combined with other materials, such as dextran microparticles, to create a controlled-release system that maintains growth factor activity over time [19]. Hydrogels can also be designed to mimic the natural extracellular matrix, which helps maintain growth factor activity and promote cell adhesion and proliferation [22]. The choice of a specific method to ensure the stability and activity of growth factors in hydrogels depends on the specific application and the desired properties for bone regeneration.

Some potential disadvantages of using hydrogels in bone tissue regeneration include low mechanical strength, limited control of degradation rate, risk of inflammation, difficulty achieving optimal porosity, and limited long-term stability. The low mechanical strength of hydrogels may limit their application in tissue engineering [60]. Controlling the rate of degradation of hydrogels is difficult, which can affect the release of growth factors and other therapeutic agents [62]. In some patients, hydrogels may cause an immune response or inflammation, which may reduce the effectiveness of treatment [58]. Achieving optimal porosity in hydrogels can be challenging, which can affect the diffusion of nutrients and regenerative growth factors necessary for bone regeneration [27].

Speaking about the porosity and permeability of hydrogels, we can say that their porosity ensures the penetration of cells and blood vessels into the gel matrix [16,33,36]. This allows bone cells to grow and multiply within the hydrogel, allowing for more efficient bone regeneration. The permeability of hydrogels is also important for nutrient exchange and metabolic waste removal [23,52].

Hydrogels can be designed to be highly biocompatible, meaning they do not cause negative reactions in the body. In addition, hydrogels can be biodegradable, that is, they can decompose within the body over time, gradually giving way to newly formed bone tissue [29,46].

These fundamental properties of hydrogels make them promising materials for use in bone regeneration, providing support for cellular activity, delivery of regenerative growth factors, and creation of an optimal environment for effective bone tissue repair.

In conclusion, it should be noted that hydrogels represent a promising group of materials for inducing bone tissue regeneration. Their unique properties, such as a water-gel structure, the ability to deliver regenerative factors in a controlled manner, and the ability to be engineered and modified, make them effective tools for stimulating bone regeneration.

4. Conclusions

In conclusion, it should be noted that hydrogels represent a promising group of materials for inducing bone tissue regeneration. Their unique properties, such as a water-gel structure, the ability to deliver regenerative factors in a controlled manner, and the ability to be engineered and modified, make them effective tools for stimulating bone regeneration.

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