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The Benefits of Application of Hydrogel in Bone Grafting Technology

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Abstract

Bone plays a pivotal role in safeguarding organs, supporting bodily structures, and maintaining calcium homeostasis. Injuries to bones or bone disease often necessitate interventions for bone repair, such as bone grafts. Autografts and allografts are currently the most promising techniques, but they exhibit limitations, which prompts the exploration of alternative solutions, particularly artificial bone graft materials. This paper examined the potential of hydrogels as a groundbreaking alternative to traditional bone graft materials. In order to properly assess the promise of this new technology, recent advancements in hydrogels are explored here, paying particular attention to whether hydrogels are capable of overcoming the limitations of current bone grafting methods. As a result, hydrogels show significant promise as bone graft materials due to their mechanical strength, biocompatibility, and unique properties like injectability and temperature sensitivity. They can effectively fill irregularly shaped bone defects and support bone regeneration by mimicking the natural extracellular matrix and incorporating bioactive elements like Mesenchymal Stem Cells (MSCs). Their potential for minimal invasiveness and gradual degradation offers advantages over traditional bone grafts. However, challenges such as variable performance and experimental limitations still need to be addressed through further research. Hydrogels yield promising findings due to their helpful and unique qualities in aiding bone regeneration. Hydrogels demonstrate strong potential as bone graft materials due to their mechanical strength, biocompatibility, and injectability, allowing for minimally invasive application. They effectively support bone regeneration by mimicking the natural extracellular matrix and incorporating bioactive elements such as Mesenchymal Stem Cells (MSCs). Their ability to degrade gradually as new bone forms offers an advantage over traditional grafts, though further research is needed to address performance variability and optimize their use. By comparing the latest research findings, this report highlights the potential of hydrogels in revolutionizing the field of bone grafting. The injectable nature of hydrogels, coupled with their ability to serve as carriers for cells, drugs, or proteins, puts them in a promising field for future bone regeneration techniques, offering a safer and less invasive alternative to traditional interventions.

Keywords: Hydrogel, Bone graft, Tissue regeneration, Periodontics, Bone loss, Periodontitis

1. Introduction

Bone is a rigid and mineralized connective tissue that protects organs and supports the body. Not only are they crucial for movement, but they also provide other important functions, such as regulating the homeostasis of calcium and providing a source of hematopoietic stem cells. Frequently, bones are injured during outdoor activities, as well as by trauma caused by road traffic accidents and disease. In serious cases, such as diseases and complex fractures when the bone tissue cannot heal itself, intervention for bone repair, such as bone graft, is needed.

A bone graft is a surgical procedure that uses transplanted bone or synthetic materials to rebuild or reconstruct

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diseased and damaged bones, healing bone loss occurring from disease or injury. The bone graft material can be harvested from the patient's body, provided by a donor, or be made of a synthetic material. At the present time, autografts (bone tissue harvested from the same patient) are the most promising technique for successful bone grafts. However, explantation of living bone tissue comes with several limitations including limited availability and the risk of morbidity and pain at the site of the transplant (Fernandez de Grado et al. 2018). This makes artificial bone graft materials especially important, as they have the potential to overcome the flaws of autografts and provide a safer and painless bone graft procedure. A current example of artificial bone grafts is synthetic porous substitutes; however, they have disadvantages such as brittle properties and poor performances in certain medical conditions. Another material used is calcium sulfate, which has significant drawbacks due to its fast resorption and non-osteoinductive structure and can cause infection in certain clinical conditions.

Hydrogels offer a promising alternative to synthetic bone graft material for several reasons. Since Hydrogels are made of three-dimensional hydrophilic polymer chains which indicate better mechanical strength and can replicate the bone's natural extracellular matrix (ECM) (Xin Bai, 2018), we anticipate that this should make them well-suited for endogenous cell growth. We also predict that unique features of hydrogels, unlike synthetic porous substitutes, give hydrogels advantages over their counterparts such as injectability, which makes them suitable for irregularly shaped bone defects and enables minimally invasive surgeries. Hydrogels can be synthesized from natural materials, including polysaccharides like chitosan, hyaluronan, and alginate, as well as proteins such as fibroin, collagen, and gelatin, which make them more diverse (Xin Bai, 2018). We also predict that these natural polymers will be advantageous in promoting cell adhesion, growth, and tissue regeneration. Since they are made of similar components as the natural extracellular matrix (ECM) or closely resemble them, they should offer excellent biocompatibility, minimal immune response, and low cytotoxicity. Currently, the cost of hydrogel injections varies widely depending on the composition of the gel, insurance coverage, and where one receives medical treatment (*SpaceOAR Hydrogel Injection*, n.d.). As this method of treatment becomes more popular, however, cost is expected to become more normalized and affordable.

Hydrogels are materials that swell but do not dissolve in water, maintaining a distinct 3D network structure (Tommasi et al. 2016). They are made of hydrophilic polymers that mimic the composition of biological tissues. They can be used to deliver cells, drugs, or proteins and have even been used for bone regeneration, for instance, as a scaffold material that transports cells to certain sites (Liu et al. 2022). When combined with mesenchymal stem cells (MSCs), hydrogels—hydrophilic polymer networks that have a high water absorption capacity—provide a flexible and biocompatible scaffold for biomedical applications. They support cell survival, proliferation, and the controlled release of therapeutic agents, enhancing tissue regeneration and repair. Lipid-based nanoparticles are a highly adaptable delivery material in nanomedicine, as they may be created for targeted and controlled release of medications, genes, or vaccinations. They are also biocompatible, making them a potential alternative.

Although studies of various combinations of hydrogels with additives show promising results, many researchers are more excited by their potential for aiding bone regrowth. One characteristic that makes them advantageous is their injectability which means they can easily fill in irregularly shaped bone defects or damage and can be applied using minimally invasive surgeries compared to a 3D scaffold (Tommasi et al. 2016). Thus, injectable hydrogels have a double advantage over autologous bone grafts: they require no invasive surgery for implanting the gel or secondary surgery to remove it.

The goal of this report is to review and compare the latest research and technology in the field of bone grafting and outline the role hydrogels may play in the future of this rapidly evolving field. In order to properly assess the promise of this new technology, recent advancements in hydrogels are explored here, paying particular attention to whether hydrogels are capable of overcoming the limitations of current bone grafting methods.

2. Materials and Methods

This review was conducted by searching an online database of journal articles for relevant material spanning from late 2008 to 2024 and analyzing them accordingly within the context of bone grafting treatments and technology. Specific search engines that were used include Google Scholar (https://scholar.google.com/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/). These were chosen because they focus on published peer-reviewed research studies, indicating a level of quality and review that we were looking for. Some common search terms we used to refine the results included: hydrogels in tissue engineering, hydrogel scaffolds, and bone regeneration. Some of the journals that published papers referenced in this review include: *Journal of Tissue Engineering*, *Bioactive Materials*, *Organogenesis, and Oncotarget.*

Articles/journals were selected to be included in this review based on credibility which was assessed in a couple of ways. First, we confirmed that the published article underwent a peer-review process by researching the journal (resources such as https://www.mdpi.com/ were used to confirm details about the journal). Next, we made sure that there were no retractions to the articles included since those indicated questionable results. Lastly, each article was briefly screened to determine its reliability which included assessing the quality of the other studies referenced and the logic of the experimental design. Information taken from outside sources included mainly trends and conclusions which were based on numerical data and quantifiable findings.

3. Results

3.1 The Science of Bone Grafts

A bone graft is a surgical procedure to transplant new bone tissue or similar substances to rebuild damaged or diseased bones. There are different types of bone grafting: autograph, which takes the bone from the patient's body, allograft, which uses bone from a donor, and bone graft substitute, which uses synthetic materials that the body can absorb over time. However, each has its own limitations (Table 1) as an autograph requires additional surgical procedure to acquire the bone from the patient's own body. Allografts are often costly and have a high chance of disease transmission, and also incorporate slowly into the patient's body (Roberts et al., 2012). Finally, synthetic bone grafts have disadvantages such as brittleness and tend to have a lower success rate compared to the other types of bone grafts (Roberts et al., 2012). Hybrid grafts which are made by combining synthetic bone substitutes with bone marrow, are an important part of the future of bone graft technology as it utilizes osteogenic cells and growth factors that induce bone regrowth (Zhao et al., 2021).

Table 1. The Advantages and Disadvantages of Bone Grafting Materials.

Grafting methods	***Advantages***	***Disadvantages***
Autograft - *Comes from the patient's own body*	*Higher chance of successful fusion, no risk of disease transmission, shorter healing time*	*Limited supply, additional surgical procedures*
Allograft - *Donated material*	*No need for additional surgery, higher availability, no risk of donor site complications of recipient*	*Risk of disease transmission, slower incorporation, higher cost*
Synthetic - *Uses synthetic materials instead of live bone*	*Sterile, no chance of disease or pathogen transference, unlimited sizes and shapes*	*Inconsistent performance in different clinical conditions/resorption, brittle properties*

3.2 New Hydrogels

The very first reference to hydrogel was made in 1894 (Lee et al., 2012). Hydrogels in that period referred to a colloidal gel of inorganic salt. Although different from the modern type of hydrogels, it is highly intriguing that it was mentioned at such an early time. The hydrogel of modern understanding was developed by Wichterle and Lim in 1960 (Wichterle, 1960). Even after the functionality of hydrogels in the biomedical field was recognized, the number of publications on hydrogels was under 100 per year until 1974 (Lee et al., 2012). After the year 2000 yearly publications mentioning "hydrogels" sharply increased and publications began to appear under the topics of "smart hydrogels" and "drug delivery", as well as the use of hydrogels in "nanotechnology" (Figure 1).

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Hydrogels are advantageous especially due to their level of safety and ability to be administered to patients with minimal damage or negative impact to fill cavities. A hydrogel was utilized in an *in vivo* study involving a rat calvarial defect (Thorpe et al., 2018). Unlike conventional clinical bone grafts, this hydrogel was introduced in the form of discs, which were inserted under the skin in a defect of the femur bone, sewn up, then allowed to heal for 6 weeks before tissue was analyzed. This study found that collagen deposition and newly formed bone matrix was increased in animals where the hydrogel was injected. Specifically, "the percentage area of collagen staining was significantly increased in the centre of the defect region in comparison to sham operated controls" ($P = 0.0085$ for hydrogel without MSCs, $P = 0.0197$ for hydrogel with MSCs). This last result indicates that incorporating Mesenchymal Stem Cells (MSCs), a type of regenerative cell, into a well-suited hydrogel can not only improve integration with the surrounding bone tissue but also create a supportive microenvironment around the cells, thereby balancing their osteogenic differentiation (Thorpe et al., 2018). Furthermore, 5/7 animals tested with hydrogel displayed effective healing across the defect region of the bone.

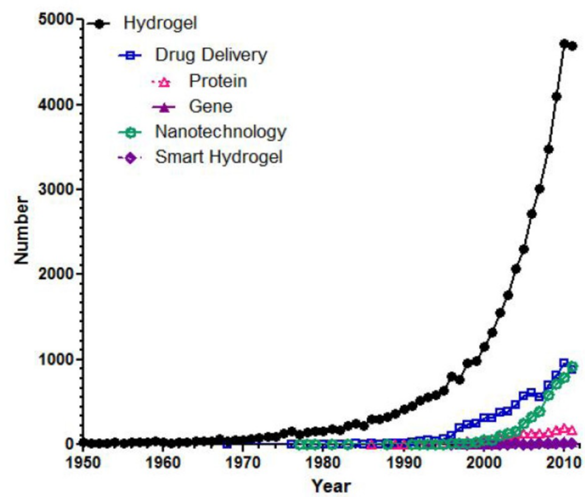

Figure 1. The Number of References Published Under a Research Topic of "Hydrogel" in SciFinder®. The total number of papers on hydrogels from 1950 to 2011 within the categories of drug delivery, (showing subtopics of protein and gene applications), nanotechnology and smart hydrogels all begin to sharply increase after the year 2000 (Lee et al., 2012).

Hydrogels can be made from different materials, and one such material that has been studied is chitosan, a naturally occurring polymer derived from the exoskeletons of crustaceans. In one study, chitosan gel was used as a carrier for Bone morphogenetic proteins (specifically rhBMP-2), in critical bone defects of 36 Wistar rat mandibles (Issa et al., 2008). Two weeks after surgery, the bone tissue was analyzed for signs of regrowth and repair and it was found that there was a statistical difference between the rhBMP-2 group versus sham group ($p < 0.05$). It was also observed that newly formed bone was more intense in the region of the defect in the Chitosan + rhBMP group. Therefore, this study concludes that chitosan gel was adequate for both defect filling and rhBMP-2 protein release to promote bone repair (Issa et al., 2008).

Another material being studied as a hydrogel is that made from silk. Silk is a natural biopolymer obtained from the silkworm Bombyx mori. Silk fibroin has been used as a bone scaffold in sponge, fiber, film, and hydrogel forms. Unlike the studies above, it has also been studied in human clinical trials. In patients who received a silk mat membrane following the extraction of a molar demonstrated significant increases in new bone (approximately 4mm) six months after the grafting procedure (Kwon, 2018; Cai et al., 2017; Kweon et al., 2017).

4. Discussion

The current limitations of various bone graft types along with the development of new grafting technology has led to a new variety of bone substitutes with different chemical structures and properties that can be adapted to different types of bone defects. In addition, some synthetic bone substitutes can combine multiple materials to create composite bone substitutes, which improve the osteoconductive properties of each material, or can be used as a carrier for useful bone growth proteins.

Hydrogels provide promising results due to their unique and effective properties, however, more research on their use in bone regeneration will be important for developing effective applications of this exciting material. There are several limitations to the presented studies, which are important to note. For example, in the in vivo study with Wistar rats (Thorpe et al., 2018) the number of rats for each group was quite small, indicating that additional studies should be done to confirm these results. In addition, although histological markers of healing were observed, few of their quantifications reached the level of statistical significance between hydrogel-injected and sham-operated controls. More animals were used in the subsequent study on Chitosan and rhBMP-2 however this study included primarily qualitative results rather than quantitative, which makes them difficult to compare to similar studies (Issa et al., 2008). In clinical studies with silk hydrogels, although the results seem promising, it has been noted that the generated membrane has good biodegradable qualities but has less than advantageous mechanical properties (being unstable)(Cai et al., 2017). Current studies are aimed at different preparations of these materials to make them more suitable for clinical use (such as those proposed by Kweon et al., 2017).

In the future, the development of osteoconductive hydrogels will likely be a focus as they will act as a scaffold to support bone growth and promote the integration of the graft with the neighboring bone tissue. Emphasis in upcoming studies may also be placed on the biodegradability and injectability of hydrogels, as these features can lead to the gradual degradation of hydrogels as new bones form, providing minimally invasive delivery methods (Almawash et al., 2022). Lastly, using hydrogels as carriers for other substances that promote bone growth and healing could potentiate its positive effects.

5. Conclusion

Although there are certainly drawbacks in the current methods of bone grafting, the introduction and study of hydrogels have provided promising results and proved to be helpful in many types of bone defects due to its flexible characteristics. As bone grafts are important in bone regeneration in humans and animals, the research on hydrogels is crucial as it may provide a better solution that overcomes the disadvantages of traditional bone graft methods. The application of hydrogels in bone regeneration has a positive future as it offers a versatile approach that could revolutionize regenerative medicine by providing precise and flexible solutions for improved bone healing.

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