Applications of Polymers for Tissue Regeneration in Medical Treatment

Ningjing Cai*

Queen Mary University of London Engineering School, Northwestern Polytechnical University, Xi'an, China

*Corresponding author: n.cai@se20.qmul.ac.uk

Abstract. Multiple types of damage to human organs can result in dysfunction and incapacity. The importance of tissue repair and regeneration in the medical industry results in high demand for tissue regeneration materials. Since the scaffolds considerably speed up the healing process, the use of tissue engineering scaffolds in the restoration of injured tissues has shown amazing potential. Due to their superior processability and biocompatibility, polymers are frequently used to build three-dimensional scaffolds. However, the main issues that restrict their widespread clinical application are their inadequate mechanical strength and unsuitable degradation rate in the bone regeneration process. Because of their superior mechanical strength, synthetic biodegradable polymer composites are used. In this research, the most frequently used polymers including polycaprolactone (PCL) and gelatine methacrylate (GelMA) were employed to create polymer composite scaffolds. And this research categorized polymer materials for tissue regeneration based on their uses in different human organs and described their physical or chemical properties. The reader is given evaluations of each material as well as prospects.

Keywords: Polymer, Functional Materials, Biomedicine.

1. Introduction

Human organs are damaged due to traumas, aging, and so on, thus they cannot regenerate except for a few such as livers or epidermis. Incomplete repair of organ function leads to dysfunction and disability, and even disability in severe cases. At present, there are three main methods to treat tissue damage: organ transplantation, regeneration of some tissues and organs, and self-repair of damaged tissues. Organ transplantation has been greatly restricted due to donor difficulties and theoretical problems. Some tissue engineering artificial organs are difficult to be used in clinical medicine because their morphology and function are far from the organs that need to be replaced. And it is often difficult for damaged tissues to self-repair. Therefore, tissue regeneration materials become the only means to restore homeostasis when organs are damaged.

Regenerative medicine, which aims at reconstructing the structure of defective tissues and organs and improving or restoring the function of tissues and organs, has been developed as the research focus. Finding approaches to comprehend and trigger tissue regeneration in the body, or engineering new tissues is the aim of regenerative medicine. Postinsult adaptive cellular reprogramming begins under physiological circumstances. Cell division and cell conversion are encouraged by this process. At present, the technical means to realize tissue and organ regeneration include surgical reconstruction, organ transplantation, tissue engineering, and in situ induced regeneration. Among them, in situ induced regeneration is to use the natural healing and regeneration process of the body to achieve the induced regeneration of defective tissues or organs through the appropriate regeneration microenvironment provided by regenerative medical materials. Growing functional tissue and regenerating new tissues are the aims of tissue regeneration. In these circumstances, 3D biomaterial scaffolds are crucial for repairing the damage. To increase cell-cell interaction, differentiation, and nutrient transfer, it is also crucial to offer mechanical stability, an extracellular matrix-like design, an appropriate surface, porosity, and a variety of pore sizes [1].

In the field of regenerative medicine, several research teams have recently produced ground-breaking studies on the use of polymers for tissue regeneration. Without adding exogenous cells or growth factors, Ding et al. successfully induced the regeneration of bone articular cartilage using 3D printing technology. It was discovered that the porosity and mechanical properties of the swelling hydrogel scaffold had a significant effect on tissue repair and regeneration [2]. The regenerative medical materials of skin, cartilage, bone and liver have been also investigated, in terms of cell compatibility, surface design and preparation technology of biomaterials, preparation and structural control of three-dimensional scaffolds, porous scaffolds, hydrogel scaffolds, and composite scaffolds, preparation of regenerative materials containing cell growth factors and genes, evaluation of biological properties and induction of tissue regeneration of these materials. Conte et al. studied the application of biodegradable polymers (BP) in dental and maxillofacial surgery, bone regeneration, and periodontal care. They can be non-toxic degraded and absorbed by the human body and can be controllably used for drug delivery, wound management, tooth repair, and tooth bone tissue regeneration [3].

One of the crucial components of a tissue engineering technique in bone and osteochondral is a scaffold. The three-dimensional structural framework it offers can facilitate vascularization and cell arrangement. This research primarily focuses on outlining some of the most recent advances in scaffold-based tissue engineering, which could be applied in regeneration of bone, osteochondral, vascular, etc. While in dental medicine, the regeneration of pulp tissue and restoration of tooth vitality may be possible with the use of biomaterial scaffolds and stem cells, which can be both secure and effective. The polymer composition as well as the methodologies will be discussed. It is important to comprehend how they contribute to the recovery. In these literatures, their optimum effects on tissue regeneration were evaluated, and their potential applications in the regenerative biomedical field were listed.

2. Application of polymers for tissue regeneration

2.1. Bone regeneration

A mechanically enhanced hydrogel scaffold based on gelatine methacrylate/gellan gum methacrylate (GelMA/GGMA) bioink and a microcarrier controlled medication release approach via photo- and ion-crosslinking was created by Li et al. [4] with sustained release of deferoxamine (DFO)-loaded ethosomes (Eth), as shown in Figure 1. The prolonged stimulation of human umbilical endothelial cells' migration and tube creation, vascularization, and osteogenesis in vivo are considerably aided by the controlled release of DFO. The Eth can be used to transport hydrophilic and lipophilic drugs intracellularly, allowing for more effective medication delivery to the circulation. In the research, GelMA/GGMA hydrogels are produced by combining phosphate-buffered saline with lithium phenyl phosphinate, followed by incubation. By modifying the bioink composition and 3D bioprinting conditions, the scaffold was bio-printed. Studies conducted in vitro demonstrated that the composite scaffold has great biocompatibility, angiogenic capability, and osteogenic potential. Moreover, composite scaffolds may induce mineralization and angiogenesis at the site of bone fractures within a rat skull bone, two important components for the healing of aberrant bone. Since it may connect vascularization and osteogenesis, a GelMA/GGMA hydrogel scaffold could provide a therapy option for bone defects.

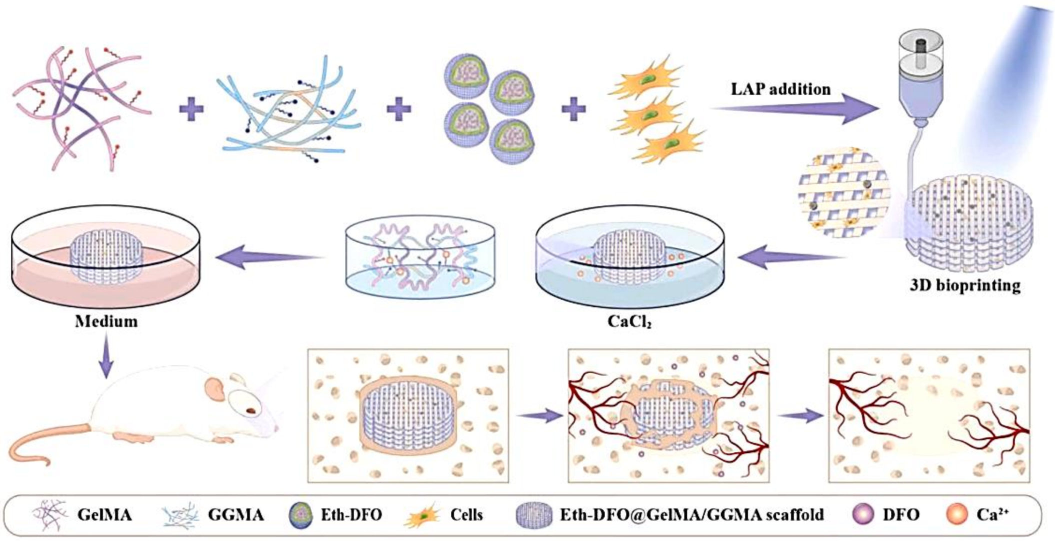

Figure 1. The process of Gel/GGMA scaffold 3D bioprinting [4]

Liu et al. used the bioprinting to prepare the PCL/SrHA scaffolds [5]. In the manufacture of bone tissue engineering scaffolds, composite materials are often used to increase the bioactivity and wear resistance of scaffolds due to the single material defects. The combination of organic and inorganic materials in composite materials can better integrate their advantages and make up for their disadvantages. At present, the inorganic materials in 3D printing scaffolds are mainly hydroxyapatite (HA). However, its degradation rate is slow and its bone induction performance is poor. Introducing the trace element Sr in the human body into scaffolds is not only conducive to improving biodegradability but also improves biocompatibility and promotes the proliferation of bone cells. In the study, the hydrothermal method was used to prepare the SrHA nanoparticles. Then the nanoparticle together with THF was mixed with dissolve PCL until the PCL/THF solution's nanoparticles were uniformly disseminated by magnetic stirring. Bone marrow-derived mesenchymal stem cells (BMSCs) from rats were cultivated to evaluate cell proliferation and osteogenic differentiation to show the efficacy of the built composite scaffolds for healing the bone. The insertion of SrHA into the 3D-printed PCL scaffold dramatically boosted cell proliferation, and BMSC differentiation was increased to higher levels on the PCL/SrHA scaffolds than the normal scaffolds that is made by PCL/HA. Conclusively, through experiments, PCL/SrHA scaffolds had the best osteogenic activity *in vivo* and had the best repair effect on damaged bone tissue. During repair, Sr ions are released and promote bone repair together with calcium ions, as shown in Figure 2. Therefore, SrHA and PCL undoubtedly constitute a good scaffold for bone tissue repair and are materials with high prospects for bone defect repair.

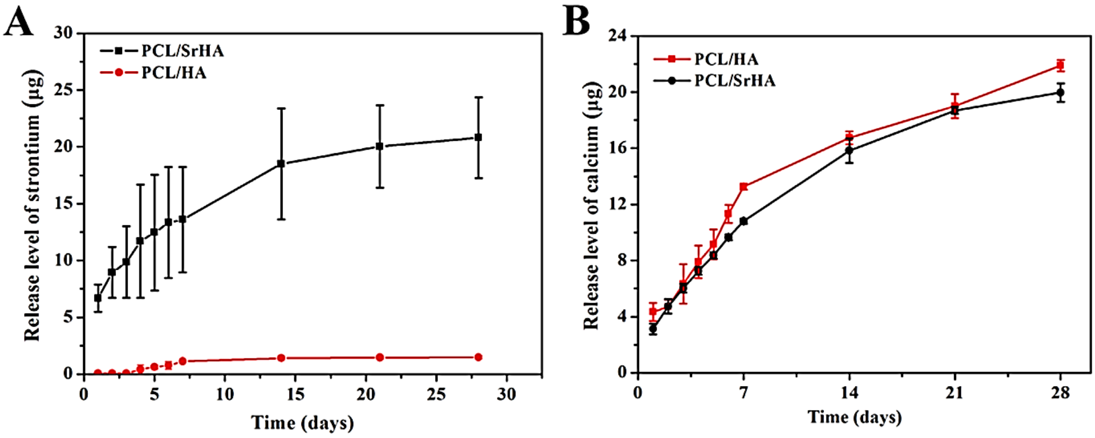

Figure 2. PCL/SrHA shows much greater ion release ability than PCL/HA scaffolds [5]

2.2. Osteochondral regeneration

Gao et al. successfully created chemically crosslinked, biodegradable gelatin hydrogels with supramolecular hydrogen bonding reinforcement PACG (poly (N-acryloyl 2-glycine))-GelMA [6], as shown in Figure 3. Due to its better biocompatibility, biodegradability, and bioactivity, gelatin gel can be used for bio-3D printing. However, GelMA, which is widely used, has poor strength and mechanical properties and cannot be used as load-bearing support. By mixing the hydrogel with organic nanoparticles and crosslinking them to enhance the mechanical strength, it can be used to construct scaffolds. By introducing PAGG, the double hydrogen bond of its side chain can enhance and stabilize GelMA. GelMA could slow down the degradation of PAGG. A biodegradable scaffold with strength was designed. At the same time, in order to improve the repair efficiency of bone damage, Mn^{2+} with biological activity was added to the scaffold. By copolymerizing ACG and GelMA, a supramolecular hydrogel ink with excellent strength was produced. Using an extrusion printing process, a bilayer biohybrid gradient hydrogel scaffold with the PACG-GelMA-Mn^{2+} cartilage layer on top and the PACG-GelMA bone layer on the bottom was precisely tuned to replicate the articular cartilage and subchondral bone structure. To fix the created high-strength structure, UV light irradiation was used to start polymerization at a cooling temperature. Proliferation, ALP activity, and differentiation of hBMSCs could be improved by adding bioactive glass (BG), and adding Mn^{2+} made it easier for the hBMSCs to differentiate into chondrogenic cells. The obtained bio-mixed gradient hydrogel scaffolds exhibited excellent performance in cartilage and subchondral bone repair. Therefore, this biodegradable bio-mixed gradient hydrogel scaffold with 3D printing has high strength and good bone tissue repair performance. It can be more widely used in the treatment of more weight-bearing tissue defects in the future.

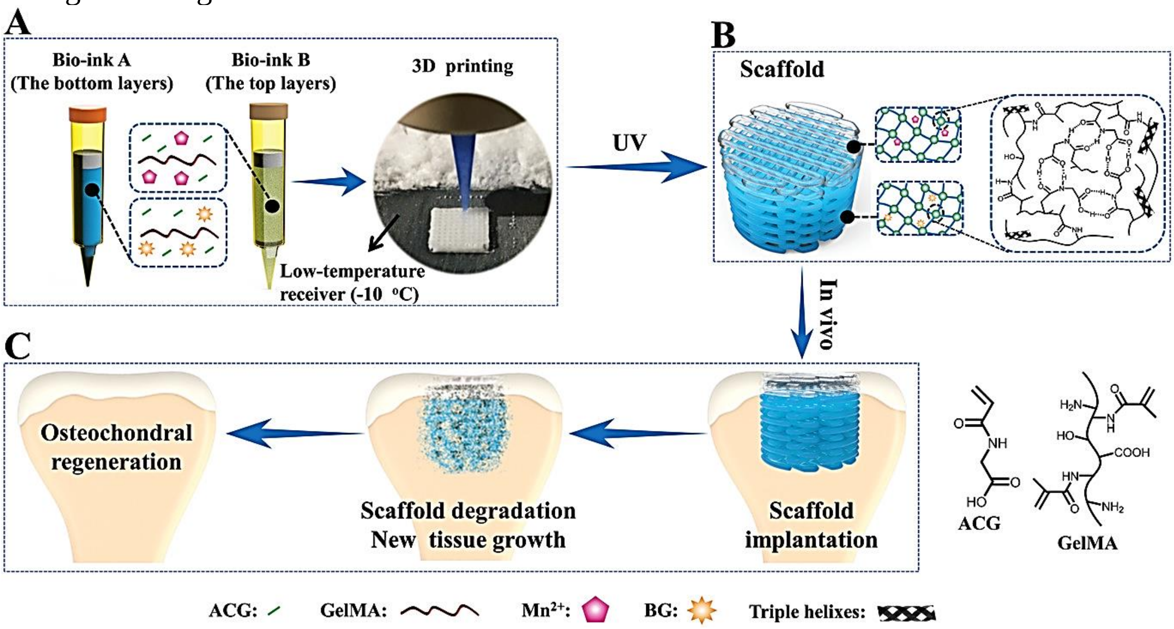

Figure 3. The scheme of 3D printed scaffolds for osteochondral regeneration [6]

Jiang et al. created a platelet-rich plasma-gelatin methacryloyl (PRP-GelMA) polymeric scaffold [7], and studied the effects of it in a rabbit model by evaluating its effect of healing the osteochondral tissue. GelMA is a kind of polymer material that is beneficial to construct biological scaffolds, but it has lower immunogenicity. Adding bioactive substances to GelMA is helpful to construct a good biological scaffold. Platelet rich plasma (PRP) is a biomaterial containing a variety of cytokines, which can promote the repair of bone tissue damage. PRP and GelMA hydrogels were prepared by resuspended GelMA at PBS, heated by water bath until it was completely dissolved. 20% and 50% PRP were added to the hydrogel, their roles in inducing the BMSCs proliferation were observed. It was found that 20% PRP had a better bone regeneration effect. The 3D-printed PRP GelMA hydrogel scaffolds have good biocompatibility and have great effects on bone tissue repair. PRP effectively creates a repair environment for osteochondral regeneration by promoting M2 polarization.

Wang et al. proposed a potential scaffold to direct the behavior of BMSCs for osteochondral regeneration and a technique for the manufacture of biomaterials for tissue engineering based on biochemical and structural modification [8]. Articular cartilage is an important connective tissue located at the end of the bone, which plays a key role in the lubrication and shock absorption of joints. But when it is damaged, its self-healing ability is limited, which will lead to more tissue damage. For tissue repair scaffolds, large pore size is conducive to bone growth, but the mechanical properties are poor. While small pore size is beneficial to induce cartilage development. Therefore, it is necessary to design large holes and small holes. 3D-printed polycaprolactone (PCL) scaffold has a high mechanical stability, and the aperture size can be precisely controlled. For the regeneration of cartilage, it is a great material. BMSCs play an important role in cartilage tissue repair. However, PCL cannot guide the behavior of biological stem cells. Sodium alginate (SA) hydrogel was introduced into the scaffold, which was favorable for the migration of BMSCs. The PCL cylinder is punched out through the 3D printing stand. SA hydrogels were prepared by ion crosslinking, SA powders were dissolved, SA solutions were prepared, and then added to each well and frozen. In the experiment, this scaffold significantly enhanced the migration of BMSCs and the differentiation of cartilage and greatly promoted the repair of cartilage tissue.

Articular cartilage serves as a surface growth plate for bones during development before being replaced by a spatially more complicated bone cartilage interface. Inspired by this, a bi-phasic cartilaginous template with fibre reinforcement were designed by Critchley et al. [9], which can be used for the regeneration of articular cartilage. In human joints, hydrogels for cartilage regeneration need to have strong mechanical properties. However, increasing the concentration of the hydrogel will have an adverse effect on the permeability and activity of cells. Different 3D-printed thermoplastics were applied to enhance the mechanical reinforcement of hydrogels to produce composite structures capable of supporting robust cartilage development. A biphasic construct composed of self-assembled MSc chondrocyte tissue was designed, laminated on an alginate saline gel containing MSCs, and enhanced with the PCL fiber network throughout the process. This promotes the ongoing development of strengthened biphasic cartilage implants used as osteochondral regeneration cartilage templates, as shown in Figure 4.

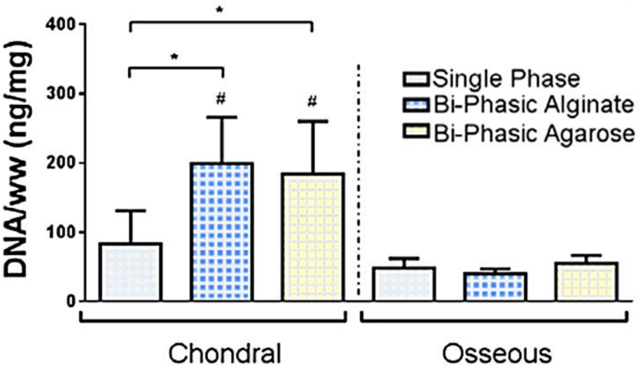

Figure 4. DNA levels substantially increased in chondral area of biphasic alginate and agarose constructions [9]

2.3. Dental resins

Tsuboi et al. produced poly (2-hydroxyethyl methacrylate/trimethylolpropane trimethacrylate) (poly HEMA/TMPT) particles to transport and release fibroblast growth factor-2 (FGF-2) for the development of dental resins that are bioactive and promote tissue regeneration [10]. Dental repairs frequently involve the use of dental adhesives. However, traditional adhesive resins cannot promote tissue regeneration. Growth factors can promote tissue regeneration, combine growth factors with adhesive resins, and by releasing active chemicals, provide them the capacity to rebuild tissues. Poly HEMA/TMPT particles are cytocompatibility and capable of releasing fibroblast growth factor-2

(FGF-2). Poly HEMA/TMPT particles were manufactured by combining HEMA and TMPT in a 90/10 weight ratio. Preparation and lyophilization of FGF-2-loaded HEMA/TMPT particles. FGF-2-loaded particles were mixed into the 4-META/MMA-based binder resin. For 14 days, FGF-2 was released from particles inserted into the resin. FGF-2 is kept alive biologically by nanoparticles implanted in resin. The findings revealed that the resin indeed aided bone repair. Therefore, this new bioactive adhesive resin has a great application prospect in periodontal tissue regeneration.

Jamalpour et al. [11] designed a hybrid construct of A layer of hydrogen is securely adhered to a polycaprolactone (PCL) membrane. Guided bone regeneration (GBR) is a good method commonly for periodontal treatment. GBR materials are classified as absorbable and non-resorbable. The non-resorbable GBR material does not require a second operation to remove it from the human body. Absorbable GBR is mainly made of natural or synthetic polymers, and polycaprolactone (PCL) is one of them. PCL has a controlled degradation rate and suitable mechanical strength. Gelatin is a good cell attractant material with biological activity and can make cells adhere better. The hybrid scaffolds of PCL and gelatin were designed. In production, the PCL film is 3D printed and the gelatin layer is attached. This structure is used for tissue regeneration of the oral cavity at the junction between bone and soft tissue. This gelatin/PCL 3D-printing film can be used to guide bone regeneration and has broad potential in interface tissue regeneration.

A three-dimensional melt electrowritten scaffolds with tissue-specific attributes were designed by Arwa Daghrery et al. [12] to guide the human-derived periodontal ligament stem cells (hPDLSCs) differentiation and mediate macrophage polarization. In periodontal regeneration, it is very important to obtain well-oriented soft tissue interfaces (PDL) fibers and alveolar bone regeneration. Additive manufacturing has been used to make scaffolds for tissue regeneration, but the effect is not ideal. Therefore, melt electrowriting (MEW) has been introduced. PCL is widely used in mew. The polymer particles are heated to form the polymer melt. The holder is printed at a set voltage. To increase the biological activity of PCL, luominated calcium phosphate (F/CAP) coating was introduced. Overall, the results show that MEW may eventually result in the creation of zonal biomaterial-mediating scaffolds that may control macrophage polarization. This method may be utilized as a tailored treatment for periodontitis and other inflammatory illnesses that require efficient tissue regeneration.

2.4. Vascular regeneration

Currently, the majority of synthetic vascular replacements are nondegradable polytetrafluoroethylene surgical grafts, which may be utilized to replace large-diameter arteries (⩾6 mm). However, polytetrafluoroethylene grafts exhibited poor patency in small-diameter vascular catheters (⩽6 mm). Many works have been done previously to solve the difficulties of small-diameter vascular. However, they all have many problems. Duijvelshoff et al. [13] developed a bioresorbable polymeric graft that can be transported through the catheter and can promote the regeneration of blood vessels. This transcatheter tissue engineered vascular grafts (T-TEVGs) were created and delivered into the abdominal aorta of rats. In manufacturing, biomaterials derived from poly-L-lactic acid are produced into fibrous catheters. After the diameter and thickness of the catheter were measured by SEM, it was cut into size and sterilized. T-TEVGs were then implanted into rats with damaged aorta. In the experiment, T-TEVGs were successfully delivered and induced regeneration of arterial vascular tissue.

3. Conclusions

In this research, the polymers for tissue regeneration applied in the repair of bone, osteochondral, periodontal, and vascular were introduced. In bone regeneration and osteochondral regeneration, hydrogel scaffolds are greatly important. As they interact with cells in a manner that promotes cellular adhesion, proliferation, growth, and mineral matrix buildup. 3D bioprinting is an effective way to produce scaffolds. GelMA and PCL were significant polymers in this review that could be used for 3D bio-print scaffolds due to their mechanical stability and better formability than other materials. In dental medicine, tissue regenerative polymer materials are used in healing periodontal tissues. Polymers were used in the forms of particles, membranes, and scaffolds to promote the regeneration of defects of bones or periodontal tissue. In vascular regeneration, a graft was designed for transcatheter delivery. This research comprehensively reviews the progress of polymer-based tissue regeneration technology and the basic specifications for designing regenerative implants. Although the 3D bioprinting technology of scaffolds has made great progress, most of them are still the results of the laboratory, and there is still a long way to go before they are really applied to medical treatment. After clinical experiments, these scaffolds, films and nanoparticles composed of tissue regeneration polymers can be really applied to treatment. With the advancement of tissue regeneration technology, the regenerative medicine of human organs will be more advanced.

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