Polymeric Biodegradable Biomaterials for Tissue Bioengineering and Bone Rejuvenation

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Abstract The necessity for multiple surgeries is decreased by tissue engineering techniques, which also lessen donor site morbidity in graft procedures. Biodegradable scaffolds are created to contain cells; as new tissue develops; it gradually replaces the biodegradable scaffold to restore full bodily function. Due to their resemblance to extracellular matrices, high biocompatibility and biodegradability, natural and synthetic polymeric materials have been used extensively in bone tissue engineering. To adapt polymeric materials to the unique needs of bone regeneration, a range of approaches have been used to modify their characteristics. This review focused on current research on collagen and synthetic polymer-based scaffolds for tissue bioengineering and bone regeneration, such as polycaprolactone, poly(glycolic acid), poly(lactic-co-glycolic acid), and poly(lactic-acid-glycolic acid) (PCL). If we can better manage the interface between the material and the surrounding bone tissue, the next generation of biodegradable materials may benefit from our understanding of how cells interact with materials.

Keywords Biomaterials · Tissue bioengineering · Bone rejuvenation

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Introduction

Artificial scaffolds that imitate natural extracellular matrix (ECM), which offers an ideal environment for cell recruitment, proliferation, differentiation, and ultimately bone regeneration, are necessary for bone tissue engineering [1, 2]. Ideal scaffolds should not trigger immunological reactions and disintegrate in a controlled manner with harmless chemicals that can be eliminated by metabolism when confronted with complicated and sensitive biological systems [3, 4]. To encourage the growth of new bone tissues, biological substances must also be included. In order to establish an ideal milieu for cell functions and to sustain the flow of nutrients and metabolites, the macro- and micro-structures (such as porosity) of the scaffolds should also be carefully engineered [5]. There are numerous requirements for scaffold design in tissue engineering. Many of these are dynamic and are still not fully understood [6]. These scaffolds should additionally have adequate mechanical qualities to give the neo-tissues the required stress environment, having both mass and biocompatible deteriorated [7]. The scaffolds should also have the necessary surface chemistry and porosity for cell adhesion [7], as well as be porous and permeable to allow the passage of cells and nutrients.

As scaffolds for bone regeneration, a variety of materials, including metals, bioactive ceramics and glasses, natural and synthetic polymers, and their composites, have been studied and used thus far [8, 9]. Numerous applications have previously employed polymeric materials and their composites [10–17]. Due to their favorable biocompatibility and biodegradability, biodegradable polymers have garnered the most attention among these applications for tissue bioengineering and bone rejuvenation [8, 9]. More notably, polymers have an extremely flexible design capacity, allowing their numerous features to be easily adjusted to match particular requirements by modifying their chemical structures and compositions [18]. For bone tissue regeneration, a wide variety of natural polymers, such as collagen, gelatin, and chitosan, as well as synthetic polymers, such as poly(lactic acid), poly(glycolic acid), and polycaprolactone (PCL), have been used. To improve their osteogenic performance, these materials are typically composited with one another or other inorganic materials, such as Hydroxyapatite (HA) [19, 20]. This review primarily looked at recent studies on collagen and synthetic polymer-based scaffolds for tissue bioengineering and bone regeneration, including polylactic acid (PLA), poly(glycolic acid), poly-lactic-co-glycolic acid (PLGA), and polycaprolactone (PCL).

Collagen-Based Scaffolds in Bone Tissue Engineering

Collagen is an essential component of the natural bone matrix and is used for bone regeneration and biomimetic applications [21]. Compared to the relatively low bioactivity of biomimetic materials, collagen has sufficient flexibility, high biodegradability, and biocompatibility. Collagen can therefore be used in a variety of ways [21].

Collagen can be obtained from a variety of sources and from different animals (such as mammals, marine organisms and invertebrates). Natural collagen has a low immunogenicity already, and chemical processing can further reduce it. Collagen regulates the activity of osteoblasts and osteoclasts through a number of signaling channels and assists in the healing of bone defects [22]. Collagen can now be used widely because to improvements in collagen extraction technology. Current research suggests that a variety of materials can be used to alter collagen-based biomimetic materials in order to enhance their biological qualities [22]. Flexible hydrogel and rigid scaffold are the two most often used kinds of collagen application. Alginate, chitosan, and hyaluronic acid are all biocompatible, hydrophilic, and biodegradable substances. By mixing chitosan, hyaluronic acid, and alginate with collagen in various ratios, collagen-based biomimetic materials can be created [23]. For instance, Becerra et al. (2022) used the solvent casting approach to create composite membranes made of chitosan, collagen, and hydroxyapatite [24]. Containing good hydroxyapatite dispersion in the organic matrix, membranes with micro and nanopores were produced. The thermal stability and thermal breakdown of the composites are improved by the addition of collagen and hydroxyapatite to chitosan. The highest cell adhesion was demonstrated by the membranes with the highest hydroxyapatite and collagen contents, and none of the manufactured membranes displayed any cytotoxicity, indicating that these materials have a significant potential for usage in tissue engineering applications. Additionally, hydroxyapatite (HA) and bioactive glass are anticipated to enhance the materials' mechanical characteristics and structural stability. Rigid scaffolds are created by cyclic freeze-drying and bio-inspired mineralization, while hydrogels are often made by combining aqueous solutions and various cross-linking agents. Collagen-based hydrogel, which is suitable for osseointegration viscosity and rheology, was created by adjusting the types and proportions of various materials. The porous structure of collagen-based hydrogel allows them to exchange substances with blood, allowing cells to receive continuous nutrient supply. By combining native collagen from the jellyfish Rhizostoma pulmo with marine gelatin that has been functionalized with hydroxy-phenyl-propionic acid (HPA), Rigogliuso et al. (2020) created an injectable marine collagen-based hydrogel [25]. Due to the ability to enzymatically reticulate utilizing horseradish peroxidase (HPR) and H_2O_2, this biocompatible hydrogel formulation has the potential to trap cells inside, without harmful consequences, throughout the cross-linking process. Additionally, it permits modifying the hydrogel stiffness by changing the H_2O_2 concentration without altering the concentration of polymer precursors. Following that, morphological analyses of cell phenotypic, GAG production, and cytoskeleton organization were used to assess the maintenance of differentiated chondrocytes in culture. Additionally, the enhancement of the chondrogenic gene expression program was supported by gene expression profiling of differentiation/dedifferentiation markers (Fig. 1). In order to use autologous chondrocytes in regenerative medicine procedures, this gives a viable technique for retaining the cellular phenotype in vitro in combination with the biochemical characteristics of marine collagen.

Collagen-based scaffolds also have better compressive strength, stiffness, and pore structure when mixed with other materials, which can considerably enhance

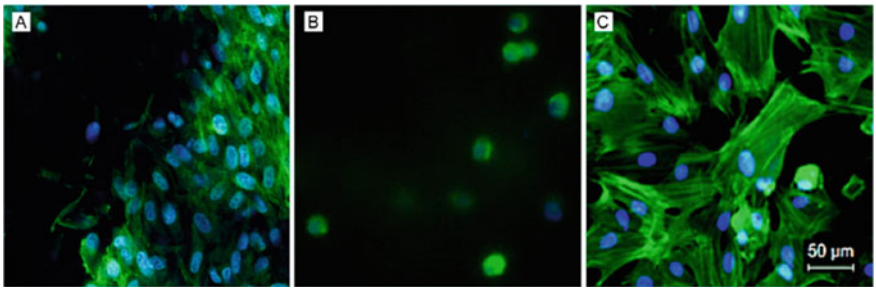

Fig. 1 Culturing in MCh does not alter cytoskeleton organization and NCs express markers of the differentiated state. Staining of NCs after 8 days of culture, respectively, within RTCh (**a**), MCh (**b**), and 2D (**c**) [25]

the efficacy of bone healing. Through a number of signaling pathways, bioactive substances, such as chemicals, cells, and growth factors, can encourage the osteogenesis and angiogenesis of scaffolds [26]. For instance, by activating the SMAD and MAPK pathways, the bone morphogenetic protein 2 (BMP-2) can encourage the differentiation of bone marrow stromal cells (BMSCs) into osteoblasts [27]. Hydrogel made of collagen is frequently utilized as a delivery system. The continual release of bioactive chemicals to the local part is made possible by the breakdown and diffusion of the gel. The release rate and breakdown rates of collagen-based hydrogel can both be adjusted by adjusting the proportions of various components [28]. Bioactive ingredients were loaded into collagen-based scaffolds using physical mixing and electrostatic adsorption to promote regional bone repair [29]. Numerous collagen complexes have so far been examined in vitro for bone repair [30]. To confirm the viability of these scaffolds, comprehensive in vivo tests are still lacking. In order to accomplish flawless bone regeneration, it is still difficult to develop composites that can meet all the necessary parameters, such as porosity, pore size, biocompatibility, mechanical integrity, structural stability, bone conductivity, and osteoinductivity [30]. The internal and external multi-layered complex structure of real bone, as well as the natural condition of bone regeneration, cannot yet be precisely replicated by any technology. The clinical success of composite collagen-based materials in bone regeneration is just around the corner thanks to the advancements in bioprinting technology, tissue engineering, and biomimetic mineralization.

Bone-Tissue Scaffolding Using Synthetic Polymers

In order to allow for regenerated bone to replace the support lost from the scaffold, the delicate interplay between mechanical support and degradation time must be regulated because of the specific mechanical requirements of bone-tissue scaffolds [31]. For bone regeneration or osteoinductivity, a porosity of between 80 and 90% and a pore size greater than 300 m are desirable. By including osteoinductive, or growth,

substances that can be released during deterioration, this may be improved [32]. Collagen, a polymer, and the inorganic ceramic apatite are the two main components of natural bone [33]. By simulating this natural environment with composite scaffolds made of both polymeric and inorganic phases, regeneration may be facilitated [34]. Several polymers and polymer composites have been used to create clinical-grade scaffolds that have been successful in bone regeneration and have led to the development of commercial products [35]. These scaffolds have the optimal characteristics for bone-tissue engineering applications. Aliphatic polyesters such polylactic acid (PLA), poly(glycolic acid) (PGA), poly-lactic-co-glycolic acid (PLGA), and polycaprolactone (PCL) have been used to the greatest extent due to receiving US FDA approval. Following a summary of specific research publications that accelerated commercial development, samples of various goods that are currently on the market are provided [36].

With biopolymers serving as viable carrier options in addition to their application as scaffolds, suture threads, screws, pins, and plates for orthopedic procedures, there is growing interest in creating long-lasting medicine formulations for horses. Focusing on the prolonged biocompatibility and biodegradation of PLA produced by hot pressing at 180 °C, Carvalho et al. Six samples were implanted subcutaneously on the lateral surface of the neck of one horse [37]. For 24–57 weeks, the polymers stayed inside the body. The mechanical nociceptive threshold (MNT), plasma fibrinogen, and physical examination were carried out. The materials were taken out for histochemical analysis using hematoxylin–eosin and scanning electron microscopy after 24, 28, 34, 38, and 57 weeks (SEM). No significant clinical changes occurred. MNT reduced following the implantation operation and then resumed normal levels after 48 h. Histopathologic analysis up to 38 weeks revealed a foreign body response. No polymer or fibrotic capsules were seen at 57 weeks (Fig. 2). With an increase in the median pore diameter, SEM surface roughness indicated a biodegradation process. The polymer could not be found 57 weeks after implantation, just like in the histological evaluation. PLA degraded in a biocompatible manner, and these results may help guide future biomedical research.

A major advancement in bone tissue engineering has been the development of three-dimensional (3D) printing technology, which is renowned for its exceptional customizability. Growth agents, like bone morphometric protein 2 (BMP-2),

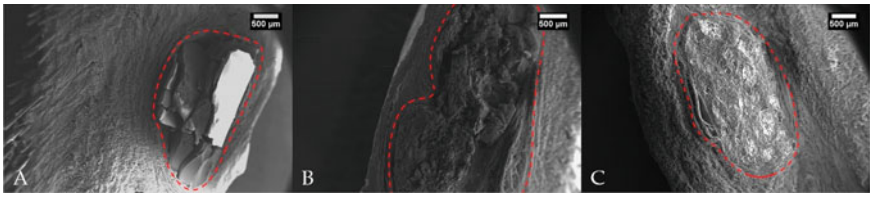

Fig. 2 SEM micrographs of skin fragments with PLA implanted in one horse **a** 34 weeks following implantation; **b** 38 weeks following implantation; and **c** 57 weeks following implantation. Dotted red lines delimits the area of the implants [37]

whose effects on bone regeneration have been extensively researched, were typically included to the 3D printed scaffolds. Cha et a. In a rat model for calvarial defects and an ectopic ossification (EO) model, (2021) examined the impact of a different shape of PLA cage/Biogel scaffold as a carrier of BMP-2 [38]. With the use of BMP-2, gelatin- and alginate-based Biogel, and a simple commercial 3D printer, the PLA scaffold was created and used to stimulate bone repair. A PLA scaffold, a PLA scaffold with Biogel, a PLA scaffold filled with BMP-2, and a PLA scaffold with both Biogel and BMP-2 were examined in vitro and in vivo, respectively, in the experimental groups. If a statistically significant difference exists between groups, it was found using one-way ANOVA with Bonferroni post-hoc analysis. The in vitro results demonstrated that the cage/Biogel scaffold released BMP-2 in a sustained slow-release pattern after an initial burst release (Fig. 3). At least 14 days passed before the released BMP-2 lost its osteoinductivity. According to the in vivo findings, in both the rat calvarial defect model and the EO model, the cage/Biogel/BMP-2 group had the highest bone regeneration. Particularly, the EO model's implanted sites exhibited more frequent bone regeneration, indicating that the cage and Biogel had a remarkable capacity to regulate the morphology of regenerated bone. In summary, the 3D printed PLA cage/Biogel scaffold system was demonstrated to be an effective BMP-2 carrier that caused considerable bone regeneration and generated bone growth in accordance with the planned shape.

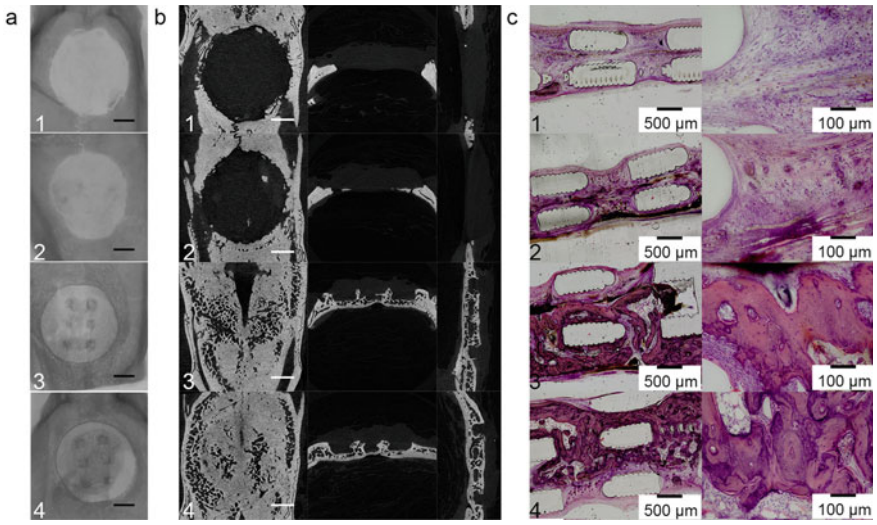

Fig. 3 In vivo result of rat calvaria. **a** PLA cage/BMP-2 group and PLA cage/Biogel/BMP-2 group both showed significant bone regeneration. Scale bar: 2 mm. **b** Cross-sectional images of rat calvaria. Both the groups with BMP-2 showed bone regeneration that bridged both edges of defect. Scale bar: 2 mm. **c** Histology sections of rat calvaria. The histology sections confirmed the results of micro-CT. Groups: 1, PLA cage group, N = 9; 2, PLA cage/Biogel group, N = 11; 3, PLA cage/BMP-2 group, N = 12; 4, PLA cage/Biogel/BMP-2 group, N = 9 [38]

Inorganic material has been added to scaffolds in several research areas to promote biomimicry and bone tissue regeneration. A PGA/hydroxyapatite composite has successfully improved bone regeneration capacity in vivo. A key component of bone grafts for the regeneration of hard tissues is hydroxyapatite (HAp). Sintered HAp, however, has poor mechanical and formability characteristics. To study physicochemical qualities and bone regeneration ability, Yeo et al. (2020) 3D-printed porous PGA/HAp composite scaffolds of various mixing ratios utilizing computer-aided modeling with poly(glycolic acid) (PGA) and Hap and printing settings [39]. A 400 m pore size was used to generate PGA scaffolds that included HAp nanoparticles. The compressive strength, osteogenesis, mineralization, and biodegradation of PGA/HAp scaffolds containing 12.5 wt% HAp were all quite high. 8 weeks following surgery, the PGA/HAp group in in vivo animal tests showed higher bone mineral density and 47% bone regeneration (Fig. 4). The PGA/HAp composite scaffolds were encircled by thick osseous tissue formations, as seen in the enhanced bone development. A workable solution to encourage patient-specific bone regeneration might be 3D-printed PGA/HAp scaffolds.

By comparing PLLA/PCL (poly-L-lactic acid/polycaprolactone) with PLLA scaffolds used in bone regeneration, Weng et al. [40] looked at the viability of PLLA/PCL. To test the implants' capacity to remodel bone, 30 mature and healthy New Zealand rabbits with a 15 mm distal ulna defect model were chosen and then randomly divided into three groups: group A (repaired with PLLA scaffold), group B (repaired with PLLA/PCL scaffold), and group C (no scaffold). Micro-CT analysis showed that group B in three groups had the best potential to regenerate bone. In group B, the surgical site's bone mineral density was higher than in group A but lower than in group C. While this was going on, both groups A and B's bone regeneration showed symptoms of inflammation due to the scaffolds' initial rapid breakdown. Overall, PLLA/PCL scaffolds in vivo initially disintegrate quickly and were more effective at repairing bone defects in New Zealand rabbits than PLLA. Further studies were required to optimize the composite for bone regeneration due to the poor mineral density of new bone and the quick breakdown of the scaffolds.

Poly lactic acid (PLA) and poly glycolic acid are copolymers that are used to make polyester (PGA). It is one of the best-defined biomaterials for enhancing bone regeneration that is currently available. The biodegradability of poly(lactic-co-glycolic acid) (PLGA) makes it one of the most popular biopolymers for tissue regeneration. However, there are significant clinical issues since the byproducts of PLGA make the implant site's environment acidic. Osteogenesis, angiogenesis, and the control of excessive osteoclastogenesis are key elements in bone repair. To enhance anti-inflammatory capacity and osteoconductivity, Kim et al. (2021) mixed the porous PLGA (P) scaffold with magnesium hydroxide (MH, M) and bone-extracellular matrix (bECM, E) [41]. Also included in the preexisting PME scaffold was the bioactive polydeoxyribonucleotide (PDRN, P). Due to the interaction of the PDRN with the adenosine A2A receptor agonist, which up-regulates the expression of vascular endothelial growth factor (VEGF) and down-regulates inflammatory cytokines, the prepared PMEP scaffold has pro-osteogenic and pro-angiogenic effects as well as inhibits osteoclast activity. For human bone marrow

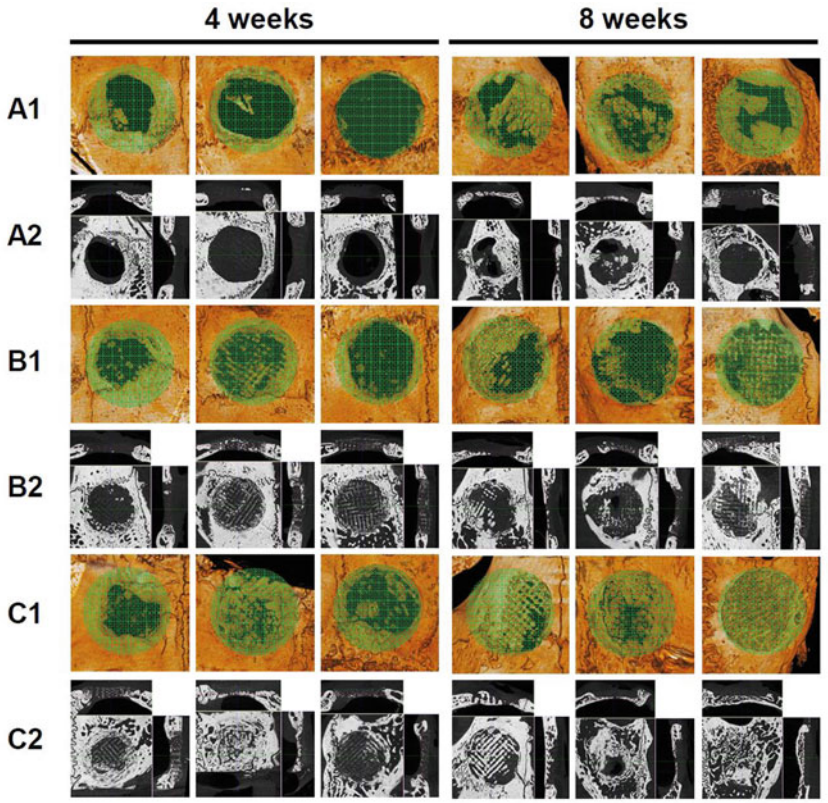

Fig. 4 Micro-CT images of the top surfaces (A1–C1) and perpendicular and horizontal sections (A2–C2) of control (**a**), PGA (**b**), and PGA/HAp 12.5 wt% composite (**c**) scaffold groups 4 and 8 weeks after surgery [39]

mesenchymal stem cells (hBMSCs) adhesion, proliferation, and osteogenic differentiation in vitro, the PMEP scaffold has better biological capabilities. Additionally, hBMSCs' gene expressions associated to angiogenesis and osteogenesis increased on the PMEP scaffold, while inflammatory factors reduced. In summary, it offers a promising method and clinically viable candidate for regenerating bone tissue and fixing bone abnormalities.

Using a poly-lactic-co-glycolic acid (PLGA) electrospun scaffold with added silica nanoparticles, Yang et al. (2018) demonstrated that this particular scaffold enhances osteogenic differentiation in vitro by increasing bone nodule formation and collagen secretion. In a rat model, a different PLGA composite functionalized with a peptide similar to the osteoinductive bone morphogenetic protein 2 (BMP-2) was used to successfully repair a critical-sized cranial lesion [42]. The PLGA composite employed in this study is an appealing scaffold for use in human bone-tissue engineering due to its mechanical similarities and the demonstration that it may

induce osteogenic differentiation as well as bone formation in vivo. In hip replacement surgery, PLA with a metal core has been employed as a biodegradable bone graft, demonstrating that it is mechanically stable and biocompatible for effective bone regeneration [43].

Conclusion

This study mainly focused on current research on collagen and synthetic polymer-based scaffolds for bone regeneration and tissue bioengineering, such as polycaprolactone, poly(glycolic acid), poly(lactic acid), and poly(glycolic acid) (PCL). From an engineering and biological point of view, the creation of biomaterials for bone regeneration devices and prostheses is a problem. Since their biodegradable nature permits avoiding the second operation and reduction in the pain and cost for patients, degradable materials for bone repair and regeneration are actively sought after and generate a great deal of interest in the field of biomaterials research. Biodegradable materials made of natural and manmade polymers are already used in healthcare settings. Diverse biomaterials have different mechanical characteristics, biological behaviors, and biodegradation mechanisms. This field of study has particular difficulties because of the special biocompatible and biodegradable needs of tissue scaffolds and the complexity of their interactions within the human body. A scaffold must not only perform and decay correctly, but it must also do so for the proper tissue type, as each has specific mechanical and morphological needs. The materials used to make scaffolds must meet a number of requirements, including having inherent biofunctionality and the right chemistry to encourage molecular biorecognition by cells and promote proliferation, adhesion, and activation. It is suggested that no single material possesses all the ideal qualities for a tissue replacement, notwithstanding the benefits and drawbacks of any unique material. Instead, tissue substitutes that meet all clinical requirements, such as the precise size and type of wound, the age of the patient, and the available preparation method, can be made using a scaffold made from a composite containing more than one natural or synthetic biopolymer, or both, depending on the situation.

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