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Review

Poly ε-Caprolactone Scaffolds: Advancements in Bone Regeneration and Grafting

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Abstract

In orthopedics and oncology, benign and malignant bone lesions pose significant clinical challenges. Malignant tumors, like osteosarcomas and multiple myeloma, pose substantial health dangers and can spread common and mostly non-life-threatening benign lesions, including non-sizing fibromas and unicameral bone cysts. Treatment plans for bone lesions may involve radiation, chemotherapy, and surgical excision, depending on their type. Combining stem cell research, bioactive materials, and advanced scaffold design, cutting-edge tissue engineering innovations provide novel approaches to bone repair. Poly ε-caprolactone (PCL) scaffolds' biocompatible and biodegradable properties have made them an important instrument in the area since they encourage the osteogenic growth of mesenchymal stem cells. PCL scaffolds encourage the adhesion, development, and specialization of cells into

osteoblasts by establishing an optimal microenvironment that replicates the conditions of actual bone tissue. Recent research indicates that PCL scaffolds are efficient in inducing the regeneration of bone tissue when subjected to osteogenic factors and other bioactive additives. This review underlines the need for PCL scaffolds to enhance the mechanism of bone healing and regeneration, thereby confirming their ability to transform the method of treating bone illnesses and accidents. Using ongoing research and pragmatic use in clinical environments, PCL scaffolds can provide unique and effective strategies to improve patient outcomes in allograft treatment.

Keywords
Biocompatible scaffolds; bone lesion; PCL scaffold

1. Introduction

Bone lesions are abnormal areas of bone tissue that can develop due to various causes. Two different types of bone lesions such as 1- Benign Bone Lesions: These are non-cancerous and typically not life-threatening for example non-ossifying fibroma, Unicameral (simple) bone cyst, and Fibrous dysplasia. 2- Malignant Bone Tumors: These are cancerous and can metastasize for example Multiple myeloma that Affects bone marrow, common in older adults [1, 2]. Commonly more prevalent than malignant bone lesions like osteosarcoma or Ewing's sarcoma are benign bone lesions including osteochondromas or unicameral bone cysts [3]. Bone lesion development can also be influenced by age, sex, and lifestyle choices [4]. A small portion of the population suffers from several rare inherited bone disorders such as fibrous dysplasia or osteogenesis imperfect [5]. Other disorders, such as Paget's disease of the bone or osteoporosis, are more frequent and affect more people [6]. The treatment of bone lesions depends on the type, location, and whether they are benign or malignant [7]. Sometimes preventing more damage needs surgical excision of the lesion. Other times, chemotherapy or radiation treatment might decrease or eliminate the lesion. For those with bone lesions, physical therapy, and pain management strategies can also assist in increasing mobility and comfort [8, 9].

Tissue engineering offers creative alternatives for bone regeneration and repair, therefore helping to treat bone defects [10]. Tissue engineering can assist in the development of tailored scaffolds and implants to encourage bone healing and integration by using cutting-edge technologies and materials [11, 12], so promoting under investigation to improve the healing capacity of injured bone tissue are stem cells and growth factors [13, 14]. These techniques provide patients with bone lesions with more efficient and customized treatment choices, therefore enhancing their quality of life and results of recovery. Furthermore, using tissue engineering methods, medications or therapeutic agents can be delivered straight to the site of the bone lesion, therefore improving the efficacy of treatment [15]. Tissue engineering can establish an appropriate environment for bone development and repair by mixing biocompatible scaffolds with bioactive materials [16, 17]. Research in this area keeps developing to create creative ideas to raise the results of bone lesion treatment and finally restore ideal bone function for patients [18, 19].

Because they give a structural framework for cell adhesion, proliferation, and differentiation (which enables wounds or damaged bone to regenerate) scaffolds are vital in tissue engineering [20]. The ideal scaffold should be mechanical load-supporting, extracellular matrix-like, and gradually break down as new bone develops. Synthetic, inorganic, and natural polymers are the three primary forms of biomaterials applied in scaffolds. About mechanical properties, processability, and biocompatibility, every group has certain particular advantages and disadvantages [21, 22]. Particularly helpful for producing complicated structures is the synthetic polymer poly ε-caprolactone (PCL) [23]. The section that follows covers PCL scaffolds; first Table 1 gives a summary of the primary material categories—emphasizing modern scaffold design advances, bioactive alterations, and their effects on osteogenic differentiation [24-26]. This review presents a comprehensive and up-to-date synthesis of recent advancements in the application of PCL scaffolds for bone tissue engineering. These developments might significantly enhance the clinical management and regenerative therapy for bone lesions.

Table 1 Advantages and limitations of Biomaterials used for scaffold synthesis.

Material Category	Examples	Advantage	Limitation
Natural Polymers	Collagen, Chitosan	Excellent biocompatibility and bioactivity	Poor mechanical strength, inconsistent properties
Inorganic Materials	Hydroxyapatite, Calcium Phosphate	Highly osteoconductive, mimics bone mineral phase	Brittle, difficult to process
Synthetic Polymers	PCL, PLA, PGA	Tunable properties, good processability	Limited bioactivity may require surface modifications

Abbreviations: PCL, polycaprolactone; PLA, polylactide; PGA, polyglycolide.

2. PCL Scaffold

Mesenchymal stem cells sometimes referred to as osteogenic stem cells, can develop into osteoblasts, chondrocytes, and adipocytes among other cell types [27, 28]. These cells are directed toward the osteoblastic lineage on a PCL scaffold by mechanical and biochemical signals given by the scaffold [29].

In tissue engineering, PCL scaffolds have become a valuable tool, particularly for the development of osteogenic stem cells. Provided by the natural extracellular matrix of bone tissue, these biodegradable and biocompatible scaffolds offer a supporting framework for cell development and colonizing. PCL scaffolds' porous architecture allows nutrients and cells to enter, thereby enhancing cell adhesion, proliferation, and differentiation. Within the framework of osteogenic stem cells, PCL scaffolds can provide an optimal environment for these cells to differentiate into osteoblasts, the bone-forming cells essential for bone regeneration and repair [30, 31].

Using PCL scaffolds in the development of osteogenic stem cells has one of the main benefits is their adjustable characteristics. The microenvironment for osteogenic development can be maximized by changing the mechanical strength, porosity, and composition of the scaffold. This adaptability enables PCL scaffolds to be tailored to meet the specific requirements of various cell

types and tissue regeneration techniques [32]. Furthermore, well-known for its slow degradation rate is PCL, which offers a continuous support system for cell development and differentiation over a long period [33].

Studies on osteogenic stem cells grown on PCL scaffolds have demonstrated improved osteogenic differentiation compared to conventional techniques [34, 35]. Including mineralized components, growth factors, or bioactive compounds in PCL scaffolds helps to increase the osteogenic differentiation of stem cells further, therefore promoting better bone tissue regeneration. PCL scaffolds present an excellent platform for encouraging the development of osteogenic stem cells and developing the discipline of bone tissue engineering [36].

In the context of regenerative medicine, PCL scaffolds are a valuable treatment for people with bone anomalies or fractures [37]. By placing a PCL scaffold loaded with osteogenic stem cells at the defect location, healthcare experts can encourage bone tissue regeneration and recovery. By providing patients with a tailored and less invasive alternative to traditional treatments like bone grafting, this approach offers them a faster and more effective means of healing and regenerating their bones [38].

In preclinical research, PCL scaffolds combined with osteogenic stem cells have shown significant promise in showing increased bone repair and functional outcomes [39]. Through scaffold property optimization, scientists can further customize its features to support the differentiation and maturation of osteogenic stem cells for clinical use. This individualized method of tissue engineering has great potential to treat a variety of bone diseases and accidents, therefore enhancing patient outcomes and quality of life. For patients undergoing regenerative medicine treatments, PCL scaffolds have various benefits. PCL's biodegradable character allows the scaffold to progressively breakdown over time, leaving behind newly generated tissue without requiring implant removal. This function ensures perfect integration of the rebuilt bone with the surrounding tissue and lowers the risk of issues related to permanent implants. Furthermore, less risk of rejection makes PCL scaffolds a safe and efficient choice for patients needing bone repair and regeneration than other materials [40, 41]. Furthermore, of great interest is 3D-printed and printed PCL systems' ability to generate very specialized scaffolds with exact control over architecture and porosity. These sophisticated manufacturing techniques improve the suitability of scaffolds for application in bone tissue engineering and other regenerative medicine domains using closely matching natural tissue structures. Their scalability and adaptability have made them a growingly significant topic of research in present tissue engineering (Figure 1) [42-44].

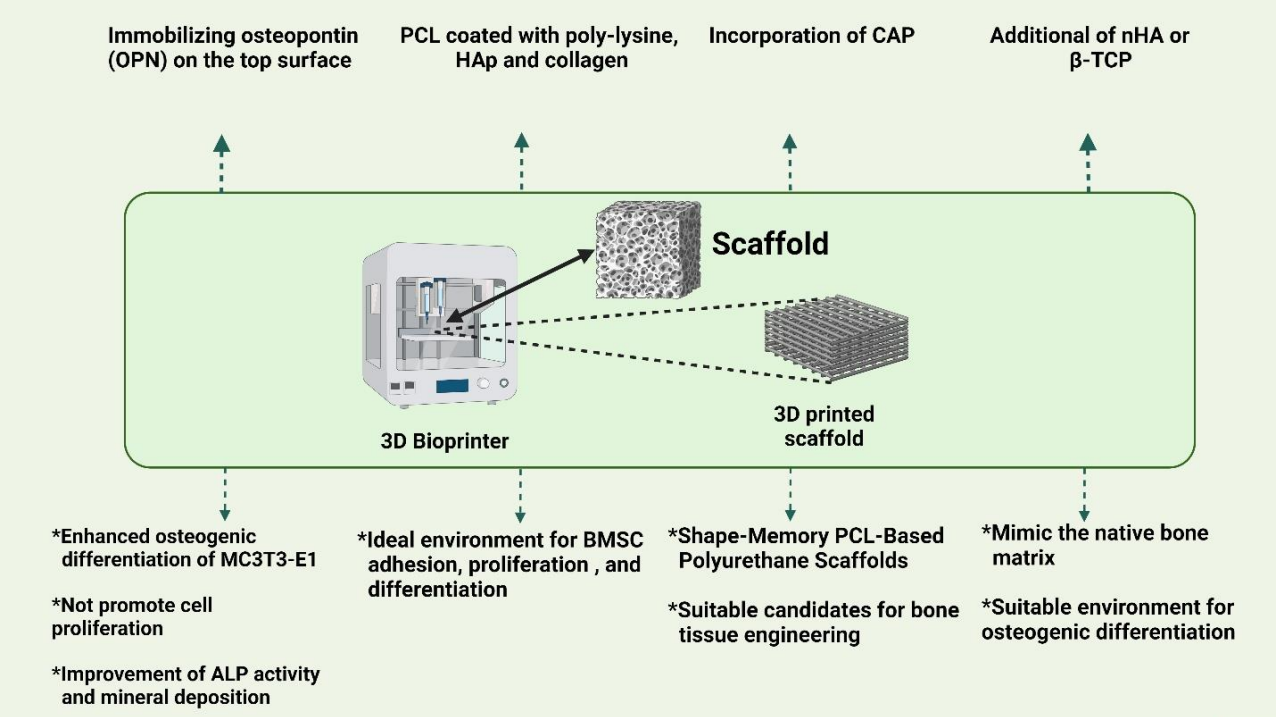

Figure 1 Schematic representation of the 3D bioprinting process used to create scaffolds for bone tissue engineering. The process involves using a 3D bioprinter to produce polycaprolactone (PCL)-based scaffolds, which are subsequently modified with various components to enhance their osteogenic potential. The printed scaffolds incorporate hydroxyapatite (HAp), collagen, and poly-lysine. They are further modified by immobilizing osteopontin (OPN) on the surface, incorporating calcium phosphate (CAP), and adding nano-hydroxyapatite (nHA) or beta-tricalcium phosphate (β-TCP). (Created by Biorender.com).

Because they are biocompatible, easy to construct into complicated forms, and have varying mechanical properties, PCL scaffolds are increasingly common in bone tissue engineering. These characteristics have made PCL a subject of much study as a substance encouraging osteogenesis and bone repair. Emphasizing how effectively they support the generation of bone tissue, Table 2 lists significant research exploring the possibilities of PCL-based scaffolds in various experimental designs [45-49].

Table 2 Summary of Key Research Studies on Bone Tissue Engineering Using PCL Scaffolds.

Scaffold and Materials	Cells Used	Experimental Details	Key Results	Author/ Reference
PCL scaffold with hydroxyapatite coating	Mesenchymal Stem Cells (MSCs)	3D-printed scaffold tested in vitro; osteogenic differentiation induced	Enhanced mineralization and ALP activity observed	Wang T, et al, 2015 [49]
Electrospun PCL nanofibers with collagen	Osteoblast-like Cells (MG-63)	Evaluated cell attachment and proliferation over 14 days	Improved cell adhesion and proliferation due to collagen integration	Niknam Z, et al, 2020 [46]
PCL/β-TCP composite scaffold	Human Adipose-Derived Stem Cells (hADSCs)	Scaffold implanted in a rat critical-size defect model	Significant bone formation and vascularization observed in vivo	Song Y, et al, 2023 [48]
PCL scaffold with bioactive glass	Primary Human Osteoblasts	Dynamic bioreactor culture used for enhanced nutrient delivery	Enhanced osteogenesis and scaffold integration	Petretta M, et al, 2021 [47]
PCL-Gelatin hybrid scaffold	Rat Bone Marrow Stem Cells (rBMSCs)	Combined PCL structure with gelatin coating to enhance bioactivity	Gelatin improved cell spreading and osteogenic differentiation	Ji W, et al, 2013 [45]

3. The Role of PCL Scaffolds in Osteogenic Differentiation

3.1 Immobilization of Osteopontin on PCL Scaffolds

Researchers have modeled PCL scaffold surfaces to improve biological interactions using layer-by-layer (LbL) deposition methods. To encourage osteogenic development, osteopontin (OPN) was immobilized on the surface of the scaffold. OPN is an essential protein involved in bone development that determines both cell adhesion and differentiation most importantly. The non-toxicity of the OPN-immobilized PCL scaffolds verified their potential use in biomedical applications. Though it did not significantly boost cell proliferation, the change significantly improved the osteogenic differentiation of MC3T3-E1 cells, shown by increased alkaline phosphatase (ALP) activity and higher mineral deposition. These results suggest a viable approach for bone tissue engineering, as OPN functionalization enhances osteogenesis without compromising cell growth [50].

3.2 Composite PCL Scaffolds for Bone Regeneration

PCL has been combined with bioceramics that stimulate osteogenic growth, such as β-tricalcium phosphate (β-TCP) and nano-hydroxyapatite (nHA), to increase bioactivity and recreate the natural bone matrix. Essential for nutrition absorption and cell penetration, linked porosity is produced when porogens such as sodium chloride (NaCl) or ammonium bicarbonate($(NH_4)HCO_3$) are introduced. Recent studies also investigate the integration of a broader range of components into PCL scaffolds, including growth hormones (such as BMPs), natural polymers (like chitosan and gelatin), and bioactive glasses, to enhance osteoconductivity, mechanical strength, and degradation rates. These hybrid scaffolds enhance cell-material interactions, thereby promoting bone healing by stimulating osteoblast formation and improving scaffold performance [51].

3.3 Biomimetic 3D PCL/Hydroxyapatite/Collagen Scaffolds

Biomimetic Another interesting approach in bone tissue engineering is the formation of 3D PCL-based scaffolds using hydroxyapatite (HAp) and collagen. This mix improves osteoinduction and promotes the adhesion and proliferation of bone marrow stromal cells (BMSCs), therefore simulating the inorganic and organic components of real bone. A coating that enhances cell adherence even further is polylysine; HAp possesses osteoconductive properties. Investigations have been conducted to enhance the mechanical and biological characteristics of the scaffold using other materials, such as silk fibroin, fibrin, or bioactive glasses [52]. Essential problems in bone regeneration can also be addressed by adding growth factors, such as TGF-β or VEGF, for controlled release, thereby enhancing osteogenesis and vascularization [45-49]. PCL-based composite scaffolds enhanced with bioceramics, natural polymers, and growth factors offer a promising approach to bone tissue engineering. Better mechanical qualities, bioactivity, and cell support for effective bone regeneration make these scaffolds like the natural bone environment. Advances in material combinations and the inclusion of growth factors are continually improving the effectiveness of scaffolds, thereby opening the path for more effective treatments for correcting bone defects [49, 53].

3.4 Shape-Memory PCL-Based Polyurethane Scaffolds

Researchers have developed form-programmable porous PCL-based polyurethane scaffolds with a memory effect; under some conditions, they might change to a predefined shape. Incorporated within these scaffolds is citrate-modified amorphous calcium phosphate (CAP), a bioactive material enhancing the osteoinductive properties of the scaffold. CAP stimulates osteoblast growth and mimics bone mineral, therefore promoting bone regeneration. Because of their unique mix of mechanical support from PCL and bioactivity from CAP, which offers both structural stability and biological signals for effective bone regeneration, these scaffolds are ideal candidates for bone tissue engineering [54].

4. Conclusion

In conclusion, osteogenic stem cell differentiation, which enables bone tissue repair and regeneration, is mainly dependent on PCL scaffolds. These scaffolds provide a suitable environment for cell development and differentiation, driving osteogenic stem cells toward the osteoblastic

lineage. By mimicking the natural bone microenvironment, which generates the creation of new bone tissue, PCL scaffolds help to express osteogenic genes and synthesize bone matrix proteins. As this field of research advances, providing patients with a quicker and more efficient alternative for bone regeneration and repair, the combination of PCL scaffolds with osteogenic stem cells has the potential to transform the treatment of bone illnesses and injuries. Future studies should, however, focus on addressing issues such as evaluating the therapeutic efficacy of these methods across a range of patient groups and optimizing scaffold properties to enhance cell integration and long-term performance.

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Author Contributions

RR: Conceptualization, writing original draft, review & editing. SH: Formal analysis, writing original draft, review & editing. KA: Provided critical editing and designed figures. KN: Validation, writing, review & editing. FF: Visualization. ES: Project administration, conceptualization, writing original draft, review & editing.

Competing Interests

The authors have declared that no competing interests exist.

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