

Research Progress in Bone Defect Repair Based on Piezoelectric and Natural Polymeric Materials

Xiangyi Ning, Jianing Nie, Yubin Pang, Weiwei Fan, Peng Wang, Jiupeng Deng*

North China University of Science and Technology, Hebei, 063210, Tangshan, China

* Corresponding author: Jiu-Peng Deng

Abstract

Natural polymer materials have attracted considerable attention in bone tissue engineering and oral and maxillofacial bone defect repair because their structures are highly similar to the extracellular matrix (ECM) in the human body. However, single natural polymer materials usually have several limitations related to osteogenesis, including insufficient mechanical properties, difficulty in controlling the *in vivo* degradation rate, and limited three-dimensional structural stability. In recent years, researchers have combined piezoelectric materials with natural polymers to mimic the microelectrical signals generated by bone tissue under mechanical stimulation. Piezoelectric ceramics, such as barium titanate, potassium sodium niobate, and zinc oxide, as well as piezoelectric polymers such as poly-L-lactic acid, can generate microelectrical signals under mechanical force. These signals can promote osteoblast proliferation and differentiation, enhance mineral deposition in bone tissue, and ultimately contribute to bone defect repair. This review focuses on the current research progress of piezoelectric materials, natural polymer materials, and bone defect repair. It summarizes the characteristics, biological mechanisms, and application advances of different materials. This review aims to promote further research on natural polymer-based piezoelectric composites for bone defect repair and improve their translational potential for future clinical applications.

Keywords

Bone defect; piezoelectric material; natural polymer; silk fibroin; chitosan; bone tissue engineering.

1. INTRODUCTION

Bone defect repair has long been a central topic in oral prosthodontics, implant rehabilitation, periodontal regeneration, and maxillofacial surgery. Although traditional autologous bone grafts, allogeneic bone grafts, and artificial bone substitutes have been widely used in clinical practice, these repair strategies still have several limitations. These include donor-site morbidity, immune rejection, mismatch between the degradation rate and the rate of new bone formation[1], and difficulty in reconstructing vascular networks[2]. With the development of tissue engineering and materials science, piezoelectric materials that can mimic the endogenous electroactive microenvironment of bone tissue have gradually become a frontier direction for regulating bone regeneration[3]. Bone tissue is essentially a dynamic coupling system with stress-induced electrical signals[4]. This property is known as the piezoelectric effect of bone. Bone remodeling is driven by the combined effects of physical and biological processes, including the mineralized matrix, cell membrane potential, and external mechanical loading. Based on this mechanism, piezoelectric materials can convert mechanical forces in the body into local electrical stimulation. This stimulation can further intervene in and regulate

osteoblast adhesion, proliferation, and differentiation[5].It can also significantly mediate angiogenesis and remodel the immune microenvironment within the body[6].

Natural polymer materials[7], such as collagen, gelatin, silk fibroin, chitosan, sodium alginate, hyaluronic acid, and cellulose, have been widely investigated as matrix materials in bone tissue engineering. This is mainly due to their excellent biocompatibility, biodegradability, and extracellular matrix-like characteristics[8].However, single natural polymer materials often show several limitations in complex body fluid environments. These include poor mechanical properties under wet conditions, insufficient stability, difficulty in controlling the degradation rate, and a lack of sustained physical stimulation. Therefore, the construction of composite coupling systems has become an important strategy. In these systems, natural polymer matrices are combined with piezoelectric ceramics, piezoelectric polymers, or natural piezoelectric structures. Such composite biomaterials can integrate favorable bioactivity, sufficient mechanical properties, three-dimensional structural support, and functional regulation through physical electrical stimulation. This strategy represents a promising development trend in the design of materials for bone defect repair[9].

2. OVERVIEW OF BONE DEFECTS

2.1. Clinical Background and Research Status of Bone Defect Repair

Bone defects in the oral region commonly result from complex pathological and physical processes, such as periodontitis, peri-implantitis, tumor resection, trauma, and infection. In the oral and maxillofacial region [10], local bone defects not only affect the anatomical foundation for subsequent implant rehabilitation, but also impair facial contour, masticatory function, and the morphology of local hard and soft tissues. Traditional repair strategies, including autologous bone grafts, allogeneic bone grafts, and artificial bone substitutes such as demineralized bone matrix, hydroxyapatite, and bioactive glass, have been widely used in clinical practice. Among them, autologous bone grafting is still regarded as the “gold standard” for bone regeneration because of its excellent osteogenic, osteoinductive, and osteoconductive properties[11]. However, these traditional approaches remain limited by several problems. These include donor-site morbidity, insufficient donor availability, and limited ability to repair defects with complex three-dimensional morphology. These limitations greatly restrict their broad clinical application.

In recent years, the design of bone repair materials has gradually shifted from passive defect filling to active induction of tissue regeneration. Under this new research direction, ideal repair materials are expected to meet multidimensional functional requirements. They should not only have good biocompatibility and a relatively controllable biodegradation rate, but also provide reliable three-dimensional mechanical support and an appropriate pore topology[12]. These properties can offer a physical and biochemical platform for cell adhesion and proliferation, osteogenic signal transmission, and precise regulation of the local immune microenvironment[13]. For guided bone regeneration (GBR), repair materials also need to have strong space-maintaining ability and an effective physical barrier function[14]. These properties help prevent rapidly growing connective tissue from prematurely invading the bone defect area[15].

2.2. Bone Tissue Mechanisms and Piezoelectric Physiological Responses

Bone is not simply a static aggregate of inorganic minerals. It is a dynamic physiological system formed by the highly organized assembly of collagen fibers, hydroxyapatite, cells, water, and various organic matrices[16]. When bone tissue is exposed to external mechanical loading, it can spontaneously generate local potential differences. This conversion between mechanical force and electrical signals is closely related to the intrinsic mechanism of bone remodeling.

This phenomenon is known as the piezoelectric effect of bone. It indicates that bone tissue can produce specific electrical signals under mechanical stress. Subsequent studies have further explained this endogenous electroactive phenomenon from multiple perspectives, including collagen conformation, spatial charge distribution, mineralized components, and bone matrix polarization.

The core mechanism of piezoelectric materials in bone repair lies in their physical response to mechanical stimulation in the body. When implanted materials receive mechanical input from the biological environment, they can generate local charges or microcurrents in situ. This process can closely mimic the physiological electrical microenvironment of natural bone tissue. Related studies have shown that [17] piezoelectric biomaterials can provide a platform for bone tissue engineering through cross-scale mechano-electrical signal conversion. This platform does not rely heavily on external environmental stimulation. Owing to their intrinsic “self-powered” and “mechano-electrical coupling” properties[5], piezoelectric scaffolds are more consistent with the local microenvironment of the body than traditional external electrical stimulation. They also provide broader potential for the translation of tissue engineering strategies into clinical practice.

2.3. Piezoelectric Material Systems and Their Characteristics

According to their physicochemical properties, piezoelectric material systems used in bone tissue engineering can be mainly divided into three categories: inorganic ceramics, synthetic polymers, and natural piezoelectric materials[18]:

Inorganic piezoelectric ceramic systems: This category mainly includes barium titanate (BaTiO_3), potassium sodium niobate (KNN), zinc oxide (ZnO), and piezoelectric hydroxyapatite composites[19]. Barium titanate (BaTiO_3)[20], has been widely introduced into mechanistic studies of bone tissue engineering because of its stable and excellent piezoelectric, ferroelectric, and dielectric properties. In recent years, multiple reviews have demonstrated the feasibility of simulating natural bone piezoelectric microenvironments through electromechanical conversion in bone tissue engineering. Potassium sodium niobate (KNN)[9], as a lead-free piezoelectric ceramic, can effectively avoid the potential biosafety risks of traditional lead-containing ceramics, such as lead zirconate titanate (PZT). Existing studies have shown that KNN has both favorable piezoelectric signal responses and good biocompatibility[21].

Synthetic piezoelectric polymer systems: This category is mainly represented by polyvinylidene fluoride (PVDF) and poly-L-lactic acid (PLLA). PVDF exhibits significant macroscopic piezoelectric properties. Its electrical output is closely related to the content and spatial distribution of the β crystalline phase within the material[22]. PLLA combines a controllable degradation rate with piezoelectric activity[23]. Its osteoinductive effect can be enhanced through specific physical processes, such as spatial orientation, uniaxial stretching, and electrospinning. It can also be strengthened by external acoustic field stimulation.

Natural piezoelectric materials and polymer composite systems[24], This category includes collagen, silk fibroin, cellulose, amino acids, and some polysaccharide macromolecules. Natural piezoelectric materials have excellent biocompatibility and low cytotoxicity. However, their piezoelectric coefficients are usually lower than those of inorganic ceramics or synthetic materials such as PVDF. Therefore, natural polymers are often used as composite matrices. A certain proportion of inorganic phases, such as barium titanate, potassium sodium niobate, hydroxyapatite, zinc oxide, or graphene, can be incorporated into these matrices. This type of composite system can effectively overcome the limitations of single materials. It can further develop into a new generation of bone repair biomaterials with both high bioactivity and stable electroactivity.

2.4. Classification of Natural Polymers and Their Composite Systems

Protein macromolecules and polysaccharide-based polymers have attracted considerable attention because their composition is highly similar to that of the extracellular matrix (ECM). These materials mainly include collagen, gelatin, and silk fibroin. Collagen is a core component of the natural bone matrix. It supports specific cell adhesion and shows good tissue compatibility. Therefore, it has been widely used as a basic material for guided bone regeneration (GBR) membranes and three-dimensional bone tissue engineering scaffolds. In addition, silk fibroin has been widely applied in different spatial structures, such as physical barrier membranes, gels, and microspheres, owing to its favorable mechanical properties, good biocompatibility, and relatively low cytotoxicity[8].

Natural polysaccharide polymers, mainly including chitosan, sodium alginate, hyaluronic acid, and cellulose, can flexibly regulate the process of bone regeneration because of their specific molecular conformations and biological properties. Taking chitosan as an example, its molecular chains contain abundant free cationic charges under physiological conditions. This physicochemical feature not only gives the material broad-spectrum antibacterial and hemostatic properties, but also provides high affinity for the early adhesion of osteoblasts[25]. However, single polysaccharide materials are prone to swelling in complex liquid environments. This can lead to a marked decrease in mechanical properties under wet conditions and make the degradation rate to control difficultly. Therefore, in ideal materials for bone defect repair, polysaccharides such as chitosan and sodium alginate are often physically or chemically combined with materials of high mechanical strength, such as hydroxyapatite[26]. This strategy can provide the required mechanical support and improve the stability of the whole composite system[27].

Current representative combinations, such as silk fibroin/chitosan, silk fibroin/collagen/chitosan, chitosan/sodium alginate, and collagen/hydroxyapatite, are designed to overcome the structural limitations of single materials through interfacial interactions between different components. These composite systems can improve the mechanical properties, surface hydrophilicity, and cytocompatibility of scaffolds. As a result, they may achieve synergistic regulation of bone regeneration in the complex and dynamic internal microenvironment of the body.

3. CHARACTERISTICS OF PIEZOELECTRIC MATERIALS AND NATURAL POLYMER MATERIALS

3.1. Bone Piezoelectric Effect and Osteogenesis-Promoting Theory

The piezoelectric effect of bone refers to the local electrical response generated under specific mechanical stimulation. This physical phenomenon is closely related to the spatial orientation and microscopic sliding of collagen fibers in the bone matrix. This finding provides a solid theoretical basis for understanding how mechanical stimulation is converted into electrical signals and further guides bone tissue remodeling. In current bone tissue engineering research, the piezoelectric effect is no longer regarded as a simple physical response. Instead, it is closely associated with cell-related molecular signaling networks[28]. A large number of studies have shown that [29] moderate microelectrical stimulation generated by piezoelectric materials can directly affect the transmembrane potential of osteoblasts and calcium ion channels. It can further activate cell adhesion and other dynamic cellular behaviors. Electrical stimulation can significantly upregulate the expression of osteogenesis-related genes. It promotes alkaline phosphatase (ALP) activity and matrix mineralization by activating key signaling pathways[30] including BMP/Smad, MAPK, and YAP/TAZ.

3.2. Application of Inorganic Piezoelectric Ceramic Systems in Bone Repair

Inorganic piezoelectric ceramic systems play a core role in electroactive bone tissue engineering scaffolds because of their unique piezoelectric output. At present, the main inorganic piezoelectric phases used in this field include the following three types.

Barium titanate (BaTiO_3 , BT): As one of the most widely studied piezoelectric ceramic materials, nanoscale BT particles can mimic the endogenous piezoelectric microenvironment of natural bone through efficient electromechanical conversion. They have shown great potential in regulating cell metabolism and inducing bone tissue regeneration. For example, chitosan/BT nanocomposite systems have been shown to have favorable electrically mediated osteogenic activity in physicochemical characterization, such as FTIR and SEM, as well as in biological evaluations[31]. Recent advanced studies have further introduced polydopamine (PDA)-modified BT nanoparticles into hydrogel networks. These studies showed that the piezoelectric stimulation released by the material can not only promote osteogenic differentiation, but also act synergistically with macrophage immunoregulatory polarization and microvascular network formation[32].

Potassium sodium niobate (KNN): Traditional lead-containing piezoelectric ceramics, such as PZT, have potential biological toxicity and the risk of heavy metal accumulation. KNN as a lead-free piezoelectric ceramic with excellent properties, can better avoid this biosafety concern. The study confirmed that KNN piezoelectric ceramics have good biocompatibility and potential for bone implantation[33]. In addition, KNN can slowly release specific ions, such as K^+ , Na^+ , and Nb^{5+} , during degradation in body fluids. This process may further help optimize the biological microenvironment of the defect area.

Zinc oxide (ZnO): ZnO has both piezoelectric properties and broad-spectrum antibacterial activity. It is often introduced into polymer matrices, such as PVDF, as an inorganic reinforcing phase. This inorganic phase can mimic the internal electric field environment of the body and promote bone defect repair. At the same time, it also shows marked antibacterial effects and can regulate the immune microenvironment[34]. This coordinated antibacterial and immunoregulatory mechanism reflects the pathological features of bone defects[35], which are often accompanied by infection and acute or chronic inflammatory responses. These advantages may further support the practical clinical application of such materials.

Therefore, nanoscale processing of inorganic piezoelectric ceramics and their uniform dispersion in natural polymer matrices with extracellular matrix-like characteristics and good biocompatibility represent a promising direction. This strategy can help construct organic-inorganic composite networks that better meet the practical needs of bone repair.

3.3. Synthetic Piezoelectric Polymers and Biodegradable Piezoelectric Scaffolds

Polyvinylidene fluoride (PVDF) is a classic synthetic piezoelectric polymer. Its highly polar β crystalline phase exhibits excellent piezoelectric response[22]. The main advantage of PVDF lies in its highly stable piezoelectric performance. Its electrospun network can also closely mimic the physical topology of the extracellular matrix (ECM). However, PVDF itself is non-degradable. This has raised clinical concerns about the long-term safety of implantation and the possible need for secondary surgical removal. In practical applications of bone tissue engineering, PVDF is more likely to be designed as a local physical barrier membrane.

Poly-L-lactic acid (PLLA) is a synthetic polymer with both biodegradability and an intrinsic piezoelectric effect. It provides a new strategy for piezoelectric materials used in bone regeneration[36]. PLLA nanofibrous scaffolds can act as a "remotely controllable bone growth stimulator" under mechanical wave stimulation, such as ultrasound. This effect is achieved through the piezoelectric response of PLLA.

Overall, synthetic polymer-based piezoelectric materials still face inherent biological limitations during clinical translation. PVDF lacks degradation kinetics, while the acidic degradation products of PLLA may cause local microenvironment acidification. Therefore, composite modification by introducing natural polymers, hydroxyapatite (HA), bioactive glasses (BGs), and other components has become a key strategy for improving the material interface.

3.4. Characteristics of Natural Polymers

Silk fibroin (SF) is a natural polymer material that has attracted increasing attention in many fields in recent years. It exhibits favorable physicochemical properties. The systematic review by Wu et al.[37] showed that SF materials have great potential for inducing bone tissue regeneration through precise structural design and surface chemical modification. A comparative study by Kim et al. [38] in a rat critical-sized calvarial defect model further confirmed that SF membranes could effectively mediate new bone deposition without causing obvious foreign body inflammatory responses. These findings indicate that SF is an ideal matrix material for three-dimensional scaffolds and also has potential as a guided bone regeneration (GBR) membrane.

Chitosan (CS) is an amino polysaccharide with wide sources[39]. It provides excellent broad-spectrum antibacterial activity, good biocompatibility, and biodegradability. However, when CS is used alone in films or scaffold structures, it is inevitably limited by excessive swelling, relatively poor mechanical properties under wet conditions, and possible acidic solvent residues during preparation[40]. Therefore, composite modification with other materials is necessary to improve its performance.

In silk fibroin/chitosan binary composite systems, SF mainly contributes favorable mechanical properties and good biocompatibility. CS macromolecules improve interfacial hydrophilicity and provide a corresponding antibacterial microenvironment. Zhou et al.[41] successfully constructed an SF/CS/nano-hydroxyapatite (nHA) biomimetic composite scaffold and confirmed its osteogenic efficacy. These studies provide strong biological and material-based support for the design of biomimetic materials composed of natural protein/polysaccharide macromolecules and inorganic phases[42].

3.5. Natural Polymer/Piezoelectric Inorganic Phase Composite Systems

The combination of natural polymers and piezoelectric inorganic phases represents a material design strategy that closely meets the physiological needs of in situ bone defect repair in current bone tissue engineering. This strategy is based on the complementary advantages of different components. Natural polymers provide an extracellular matrix (ECM)-like microenvironment and excellent biocompatibility. Piezoelectric inorganic phases act as dispersed phases and give the composite system electroactive properties and the ability to form local electrical microfields. Relatively mature biomedical foundations have been established for natural polymer-based blended macromolecular networks. Meanwhile, lead-free piezoelectric ceramics can provide efficient piezoelectric signals. They can also meet the biocompatibility requirements of bone implant materials and help build an electrophysiological microenvironment in the defect area. Therefore, this type of composite system has become an effective material support for current bone repair applications.

4. LIMITATIONS AND FEASIBILITY OF COMPOSITE MATERIALS

4.1. Limitations of Composite Materials

At present, piezoelectric bone repair materials have shown promising potential in bone tissue engineering. However, several limitations remain in material preparation, interfacial regulation,

in vivo electromechanical response, and clinical translation standards[43]. The microelectrical stimulation generated by piezoelectric materials is still difficult to precisely regulate osteoblast adhesion, proliferation, differentiation, angiogenesis, and local immune responses. The osteogenesis-promoting effect of composite material systems may be influenced by multiple factors. These include surface topology, pore characteristics, active ion release, surface hydrophilicity, and local charge distribution[44]. Natural polymer materials usually have good cytocompatibility. However, the final properties of the composite system can be affected by several material-related factors. For example, the β -sheet crystallinity of silk fibroin (SF), the degree of deacetylation of chitosan (CS), and the acidic solvent system may partly influence surface hydrophilicity and swelling behavior. In addition, oral and maxillofacial bone defects are located in a complex environment. This environment contains body fluids, blood, inflammatory factors, masticatory forces, and bacterial microenvironments. Therefore, simple in vitro piezoelectric parameters cannot fully reflect the electromechanical coupling behavior of the material after implantation. Studies should pay more attention to the evaluation of piezoelectric stability under wet conditions, dynamic mechanical loading, and long-term degradation in future. This would make experimental results closer to real clinical application scenarios[20].

After the introduction of inorganic piezoelectric particles, such as potassium sodium niobate (KNN) and barium titanate (BaTiO_3), the composite system also needs to address uneven interfacial dispersion. Nanoscale or microscale piezoelectric particles are prone to gravitational sedimentation, particle aggregation, and local concentration differences in low-viscosity polymer solutions. These problems may lead to gradient differences in elemental distribution between the upper and lower surfaces of the formed membrane. They may further cause anisotropic piezoelectric output and unstable local mechanical properties[45]. These problems may lead to gradient differences in elemental distribution between the upper and lower surfaces of the formed membrane. They may further cause anisotropic piezoelectric output and unstable local mechanical properties. This aggregation may also form microscopic stress concentration points. As a result, the material may become brittle, which can affect the macroscopic mechanical properties and microscopic biocompatibility of the biomaterial. KNN or BaTiO_3 nano/microparticles can be better dispersed in natural polymer matrices through several strategies. These include pre-wetting, ultrasonic dispersion, surface modification, and increasing the viscosity of the polymer solution. These methods can improve the dispersion stability of piezoelectric particles in the composite system[46].

4.2. Research Necessity

Traditional bone repair materials mainly focus on osteoconduction, defect filling, and space maintenance[14]. However, they provide limited ability to mimic the endogenous electrical microenvironment of bone tissue. Simple inorganic bone powders, collagen membranes, or conventional scaffold materials are usually difficult to meet multiple requirements at the same time. These requirements include osteogenesis, angiogenesis, anti-inflammatory activity, antibacterial function, space maintenance, and mechanical stability. Therefore, it is clinically necessary and scientifically valuable to develop a new type of composite material with biocompatibility, mechanical support, biodegradability, and electroactive regulatory functions.

The advantage of piezoelectric composite scaffolds lies in their ability to convert physiological mechanical stimulation into local microelectrical stimulation. In this way, they can mimic the mechano-electrical coupling microenvironment of natural bone tissue. This can not only provide a suitable interface for osteoblast adhesion and growth, but also regulate osteogenic differentiation, vascular network formation, and the local immune microenvironment through electrical stimulation.

In oral clinical conditions, chewing movement and the traction of perioral muscles can generate continuous and moderate mechanical stimulation. These movements may help

activate local microelectrical fields and further regulate bone regeneration. As a result, the material can play an active role in promoting repair at the bone defect surface. Therefore, the composite system of natural polymers and lead-free piezoelectric ceramics is not a simple material combination. Instead, it is based on the theory of mechano-electrical conversion.

From the perspective of preparation, natural polymer materials can be processed into different forms, such as membranes, scaffolds, and hydrogels. Common fabrication methods include solution casting, freeze-drying, electrospinning, 3D printing, and hydrogel crosslinking[47]. For membrane materials, solution casting is a suitable method. For large bone defects that require three-dimensional spatial support, freeze-drying and 3D printing are more suitable for constructing porous scaffold structures. For future clinical applications, the material should not only show favorable piezoelectric and osteogenic properties *in vitro*. It should also have a stable preparation process, reliable mechanical properties, suitable mechanical strength, and good shape-maintaining ability for clinical operation.

5. CONCLUSIONS

The application of piezoelectric materials in bone defect repair is based on the natural electrophysiological characteristics of bone tissue and the theory of mechano-electrical signal coupling. Inorganic piezoelectric ceramics have strong piezoelectric output capacity. Synthetic piezoelectric polymers show good potential for processing and structural modification. Natural polymer materials have excellent biocompatibility, low cytotoxicity, and extracellular matrix-like characteristics. Current research is gradually shifting from single piezoelectric materials to natural polymer-based piezoelectric composite scaffolds, multifunctional electroactive hydrogels, and personalized 3D-printed scaffolds[48].

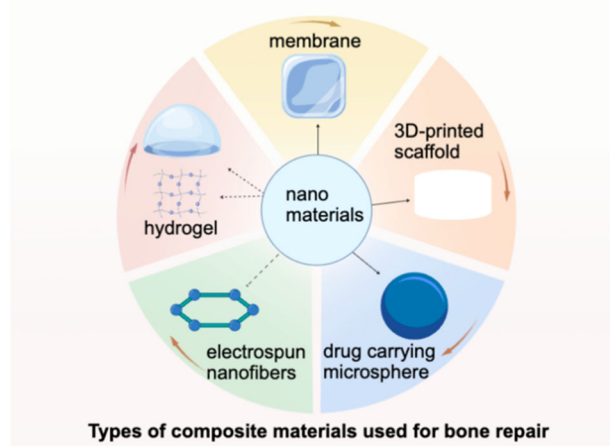


Figure 1. Types of composite materials used for bone repair

For bone augmentation and bone defect repair in oral prosthodontics, composite systems based on natural polymers and lead-free piezoelectric ceramics have potential clinical translational value. These materials can not only provide basic space maintenance and tissue support for bone defect areas, but also actively regulate multiple repair processes, including osteogenesis, anti-inflammatory responses, and antibacterial activity.

Future research should focus on several key aspects. These include the dispersion stability of nanoparticles within the material, piezoelectric performance under different environments, the biological effects of polarization treatment *in vivo*, long-term degradation safety, regulation of the immune microenvironment, and clinical operability. With continued progress in these areas,

natural polymer-based piezoelectric composites are expected to become promising biomaterials for bone defect repair and regeneration.

ACKNOWLEDGMENT

This study was Supported by the Graduate Student Innovation Fund of North China University of Science and Technology 2026S30.

REFERENCES

- [1] Amini, A. R., Laurencin, C. T., & Nukavarapu, S. P. (2012). Bone tissue engineering: Recent advances and challenges. *Critical Reviews in Biomedical Engineering*, 40(5), 363–408. <https://doi.org/10.1615/CritRevBiomedEng.v40.i5.20>
- [2] Laurencin, C., Khan, Y., & El-Amin, S. F. (2006). Bone graft substitutes. *Expert Review of Medical Devices*, 3(1), 49–57. <https://doi.org/10.1586/17434440.3.1.49>
- [3] Tandon, B., Blaker, J. J., & Cartmell, S. H. (2018). Piezoelectric materials as stimulatory biomedical materials and scaffolds for bone repair. *Acta Biomaterialia*, 73, 1–20. <https://doi.org/10.1016/j.actbio.2018.04.026>
- [4] Marino, A., & Becker, R. O. (1970). Piezoelectric effect and growth control in bone. *Nature*, 228(5270), 473–474. <https://doi.org/10.1038/228473a0>
- [5] Yang, C., Ji, J., Lv, Y., Li, Z., & Luo, D. (2022). Application of piezoelectric material and devices in bone regeneration. *Nanomaterials*, 12(24). <https://doi.org/10.3390/nano12244340>
- [6] D'Alessandro, D., Ricci, C., Milazzo, M., Strangis, G., Forli, F., Buda, G., Petrini, M., Berrettini, S., Uddin, M. J., Danti, S., & Parchi, P. (2021). Piezoelectric signals in vascularized bone regeneration. *Biomolecules*, 11(11). <https://doi.org/10.3390/biom11111622>
- [7] Filippi, M., Born, G., Chaaban, M., & Scherberich, A. (2020). Natural polymeric scaffolds in bone regeneration. *Frontiers in Bioengineering and Biotechnology*, 8, 474. <https://doi.org/10.3389/fbioe.2020.00474>
- [8] Melke, J., Midha, S., Ghosh, S., Ito, K., & Hofmann, S. (2016). Silk fibroin as biomaterial for bone tissue engineering. *Acta Biomaterialia*, 31, 1–16. <https://doi.org/10.1016/j.actbio.2015.12.009>
- [9] Chen, W., Yu, Z., Pang, J., Yu, P., Tan, G., & Ning, C. (2017). Fabrication of biocompatible potassium sodium niobate piezoelectric ceramic as an electroactive implant. *Materials*, 10(4). <https://doi.org/10.3390/ma10040407>
- [10] Zhao, R., Yang, R., Cooper, P. R., Khurshid, Z., Shavandi, A., & Ratnayake, J. (2021). Bone grafts and substitutes in dentistry: A review of current trends and developments. *Molecules*, 26(10). <https://doi.org/10.3390/molecules26103007>
- [11] Sakkas, A., Wilde, F., Heufelder, M., Winter, K., & Schramm, A. (2017). Autogenous bone grafts in oral implantology-is it still a "gold standard"? A consecutive review of 279 patients with 456 clinical procedures. *International Journal of Implant Dentistry*, 3(1), 23. <https://doi.org/10.1186/s40729-017-0082-2>
- [12] Ding, H., Cheng, Y., Niu, X., & Hu, Y. (2021). Application of electrospun nanofibers in bone, cartilage and osteochondral tissue engineering. *Journal of Biomaterials Science, Polymer Edition*, 32(4), 536–561. <https://doi.org/10.1080/09205063.2020.1846043>
- [13] Elgali, I., Omar, O., Dahlin, C., & Thomsen, P. (2017). Guided bone regeneration: Materials and biological mechanisms revisited. *European Journal of Oral Sciences*, 125(5), 315–337. <https://doi.org/10.1111/eos.12270>

- [14] Ren, Y., Fan, L., Alkildani, S., Liu, L., Emmert, S., Najman, S., Rimashevskiy, D., Schnettler, R., Jung, O., Xiong, X., & Barbeck, M. (2022). Barrier membranes for guided bone regeneration (GBR): A focus on recent advances in collagen membranes. *International Journal of Molecular Sciences*, 23(23). <https://doi.org/10.3390/ijms232314792>
- [15] Liu, J., & Kerns, D. G. (2014). Mechanisms of guided bone regeneration: A review. *The Open Dentistry Journal*, 8, 56–65. <https://doi.org/10.2174/1874210601408010056>
- [16] Yue, W., Zhang, W., Zhang, J., Qin, W., Bie, X., Zhao, Y., & Xu, G. (2025). The role of piezoelectric materials in bone remodeling and repair: Mechanisms and applications. *International Journal of Nanomedicine*, 20, 11593–11616. <https://doi.org/10.2147/IJN.S448711>
- [17] Khare, D., Basu, B., & Dubey, A. K. (2020). Electrical stimulation and piezoelectric biomaterials for bone tissue engineering applications. *Biomaterials*, 258, 120280. <https://doi.org/10.1016/j.biomaterials.2020.120280>
- [18] Zaszczynska, A., Zabielski, K., Gradys, A., Kowalczyk, T., & Sajkiewicz, P. (2024). Piezoelectric scaffolds as smart materials for bone tissue engineering. *Polymers*, 16(19). <https://doi.org/10.3390/polym16192466>
- [19] Wei, Y., Liang, Y., Qi, K., Gu, Z., Yan, B., & Xie, H. (2024). Exploring the application of piezoelectric ceramics in bone regeneration. *Journal of Biomaterials Applications*, 39(5), 409–420. <https://doi.org/10.1177/08853282231226764>
- [20] Huang, H., Wang, K., Liu, X., Liu, X., Wang, J., Suo, M., Wang, H., Chen, S., Chen, X., & Li, Z. (2025). Piezoelectric biomaterials for providing electrical stimulation in bone tissue engineering: Barium titanate. *Journal of Orthopaedic Translation*, 51, 94–107. <https://doi.org/10.1016/j.jot.2025.01.004>
- [21] Yao, T., Chen, J., Wang, Z., Zhai, J., Li, Y., Xing, J., Hu, S., Tan, G., Qi, S., Chang, Y., Yu, P., & Ning, C. (2019). The antibacterial effect of potassium-sodium niobate ceramics based on controlling piezoelectric properties. *Colloids and Surfaces B: Biointerfaces*, 175, 463–468. <https://doi.org/10.1016/j.colsurfb.2019.01.009>
- [22] Li, Y., Liao, C., & Tjong, S. C. (2019). Electrospun polyvinylidene fluoride-based fibrous scaffolds with piezoelectric characteristics for bone and neural tissue engineering. *Nanomaterials*, 9(7). <https://doi.org/10.3390/nano9070952>
- [23] Ramasamy, M. S., Kaliannagounder, V. K., Rahaman, A., Park, C. H., Kim, C. S., & Kim, B. (2022). Synergistic effect of reinforced multiwalled carbon nanotubes and boron nitride nanosheet-based hybrid piezoelectric PLLA scaffold for efficient bone tissue regeneration. *ACS Biomaterials Science & Engineering*, 8(8), 3542–3556. <https://doi.org/10.1021/acsbmaterials.2c00367>
- [24] Kamel, N. A. (2022). Bio-piezoelectricity: Fundamentals and applications in tissue engineering and regenerative medicine. *Biophysical Reviews*, 14(3), 717–733. <https://doi.org/10.1007/s12551-022-00987-9>
- [25] Liang, X., Guo, S., Kuang, X., Wan, L., Liu, F., Zhang, G., Jiang, H., Cong, H., He, S., & Tan, S. C. (2024). Recent advancements and perspectives on processable natural biopolymers: Cellulose, chitosan, eggshell membrane, and silk fibroin. *Science Bulletin*, 69(21), 3444–3466. <https://doi.org/10.1016/j.scib.2024.08.020>
- [26] Ait Said, H., Mabroum, H., Lahcini, M., Oudadesse, H., Barroug, A., Ben Youcef, H., & Noukrati, H. (2023). Manufacturing methods, properties, and potential applications in bone tissue regeneration of hydroxyapatite-chitosan biocomposites: A review. *International Journal of Biological Macromolecules*, 243, 125150. <https://doi.org/10.1016/j.ijbiomac.2023.125150>
- [27] Ressler, A. (2022). Chitosan-based biomaterials for bone tissue engineering applications: A short review. *Polymers*, 14(16). <https://doi.org/10.3390/polym14163330>

- [28] Zhang, J., Liu, C., Li, J., Yu, T., Ruan, J., & Yang, F. (2025). Advanced piezoelectric materials, devices, and systems for orthopedic medicine. *Advanced Science*, 12(3), e2410400. <https://doi.org/10.1002/advs.202410400>
- [29] Wu, H., Dong, Z., Tang, Y., Chen, Y., Liu, M., Wang, X., Wei, N., Wang, S., Bao, D., Yu, Z., Wu, Z., Yang, X., Li, Z., Guo, L., & Shi, L. (2023). Electrical stimulation of piezoelectric BaTiO₃ coated Ti6Al4V scaffolds promotes anti-inflammatory polarization of macrophages and bone repair via MAPK/JNK inhibition and OXPHOS activation. *Biomaterials*, 293, 121990. <https://doi.org/10.1016/j.biomaterials.2023.121990>
- [30] Guillot-Ferriols, M., Lanceros-Méndez, S., Gómez Ribelles, J. L., & Gallego Ferrer, G. (2022). Electrical stimulation: Effective cue to direct osteogenic differentiation of mesenchymal stem cells? *Biomaterials Advances*, 138, 212918. <https://doi.org/10.1016/j.bioadv.2022.212918>
- [31] Rotaru, R., Melinte, V., & Trifan, I. S. (2024). Biophysical stimulation for bone regeneration using a chitosan/barium titanate ferroelectric composite. *Physical Chemistry Chemical Physics*, 26(18), 13875–13883. <https://doi.org/10.1039/D4CP01240A>
- [32] Wu, P., Shen, L., Liu, H. F., Zou, X. H., Zhao, J., Huang, Y., Zhu, Y. F., Li, Z. Y., Xu, C., Luo, L. H., Luo, Z. Q., Wu, M. H., Cai, L., Li, X. K., & Wang, Z. G. (2023). The marriage of immunomodulatory, angiogenic, and osteogenic capabilities in a piezoelectric hydrogel tissue engineering scaffold for military medicine. *Military Medical Research*, 10(1), 35. <https://doi.org/10.1186/s40779-023-00466-9>
- [33] Verma, A. S., Kumar, D., & Dubey, A. K. (2020). Antibacterial and cellular response of piezoelectric Na_{0.5}K_{0.5}NbO₃ modified 1393 bioactive glass. *Materials Science and Engineering: C*, 116, 111138. <https://doi.org/10.1016/j.msec.2020.111138>
- [34] Tian, J., Paterson, T. E., Zhang, J., Li, Y., Ouyang, H., Asencio, I. O., Hatton, P. V., Zhao, Y., & Li, Z. (2023). Enhanced antibacterial ability of electrospun PCL scaffolds incorporating ZnO nanowires. *International Journal of Molecular Sciences*, 24(19). <https://doi.org/10.3390/ijms241914760>
- [35] Chen, K., Wang, F., Sun, X., Ge, W., Zhang, M., Wang, L., Zheng, H., Zheng, S., Tang, H., Zhou, Z., & Wu, G. (2025). 3D-printed zinc oxide nanoparticles modified barium titanate/hydroxyapatite ultrasound-responsive piezoelectric ceramic composite scaffold for treating infected bone defects. *Bioactive Materials*, 45, 479–495. <https://doi.org/10.1016/j.bioactmat.2025.02.020>
- [36] Chen, S., Wang, X., Zhang, D., Huang, Z., Xie, Y., Chen, F., & Liu, C. (2025). Tunable piezoelectric PLLA nanofiber membranes for enhanced mandibular repair with optimal self-powering stimulation. *Regenerative Biomaterials*, 12, rbae150. <https://doi.org/10.1093/rb/rbae150>
- [37] Wu, H., Lin, K., Zhao, C., & Wang, X. (2022). Silk fibroin scaffolds: A promising candidate for bone regeneration. *Frontiers in Bioengineering and Biotechnology*, 10, 1054379. <https://doi.org/10.3389/fbioe.2022.1054379>
- [38] Kim, J. Y., Yang, B. E., Ahn, J. H., Park, S. O., & Shim, H. W. (2014). Comparable efficacy of silk fibroin with the collagen membranes for guided bone regeneration in rat calvarial defects. *Journal of Advanced Prosthodontics*, 6(6), 539–546. <https://doi.org/10.4047/jap.2014.6.6.539>
- [39] Tuwalska, A., Grabska-Zielińska, S., & Sionkowska, A. (2022). Chitosan/silk fibroin materials for biomedical applications-A review. *Polymers*, 14(7). <https://doi.org/10.3390/polym14071424>
- [40] Sukpaita, T., Chirachanchai, S., Pimkhaokham, A., & Ampornaramveth, R. S. (2021). Chitosan-based scaffold for mineralized tissues regeneration. *Marine Drugs*, 19(10). <https://doi.org/10.3390/md19100560>
- [41] Zhou, Y., Liu, X., She, H., Wang, R., Bai, F., & Xiang, B. (2022). A silk fibroin/chitosan/nanohydroxyapatite biomimetic bone scaffold combined with autologous concentrated growth factor promotes the proliferation and osteogenic differentiation of BMSCs and

- repair of critical bone defects. *Regenerative Therapy*, 21, 307–321. <https://doi.org/10.1016/j.reth.2022.09.004>
- [42] Ye, P., Yu, B., Deng, J., She, R. F., & Huang, W. L. (2017). Application of silk fibroin/chitosan/nano-hydroxyapatite composite scaffold in the repair of rabbit radial bone defect. *Experimental and Therapeutic Medicine*, 14(6), 5547–5553. <https://doi.org/10.3892/etm.2017.5227>
- [43] Ni, X., Cui, Y., Salehi, M., Nai, M. L. S., Zhou, K., Vyas, C., & Huang, P. Bartolo, B. (2025). Piezoelectric biomaterials for bone regeneration: Roadmap from dipole to osteogenesis. *Advanced Science*, 12(32), e14969. <https://doi.org/10.1002/advs.202414969>
- [44] Joo, S., Gwon, Y., Kim, S., Park, S., Kim, J., & Hong, S. (2024). Piezoelectrically and topographically engineered scaffolds for accelerating bone regeneration. *ACS Applied Materials & Interfaces*, 16(2), 1999–2011. <https://doi.org/10.1021/acsami.3c16163>
- [45] Huang, R. H., Sobol, N. B., Younes, A., Mamun, T., Lewis, J. S., Ulijn, R. V., & O'Brien, S. (2020). Comparison of methods for surface modification of barium titanate nanoparticles for aqueous dispersibility: Toward biomedical utilization of perovskite oxides. *ACS Applied Materials & Interfaces*, 12(46), 51135–51147. <https://doi.org/10.1021/acsami.0c15216>
- [46] Sundar, U., Lao, Z., & Cook-Chennault, K. (2019). Investigation of piezoelectricity and resistivity of surface modified barium titanate nanocomposites. *Polymers*, 11(12). <https://doi.org/10.3390/polym11122013>
- [47] Li, Y., Liu, Q., & Guo, Q. (2021). Silk fibroin hydrogel scaffolds incorporated with chitosan nanoparticles repair articular cartilage defects by regulating TGF- β 1 and BMP-2. *Arthritis Research & Therapy*, 23(1), 50. <https://doi.org/10.1186/s13075-021-02438-3>
- [48] Mao, Z., Bi, X., Yu, C., Chen, L., Shen, J., Huang, Y., Wu, Z., Qi, H., Guan, J., Shu, X., Yu, B., & Zheng, Y. (2024). Mechanically robust and personalized silk fibroin-magnesium composite scaffolds with water-responsive shape-memory for irregular bone regeneration. *Nature Communications*, 15(1), 4160. <https://doi.org/10.1038/s41467-024-48404-9>