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Toward Smart Bone Healing: A Review of In Vivo Evidence and Translational Perspectives on Bioelectronic Scaffolds and Piezoelectric Biomaterials

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Abstract
The limited self-healing capacity of bones and the disadvantages of traditional grafting methods make large bone defects a significant challenge in regenerative medicine. Recent developments in bone tissue engineering (BTE) have highlighted the therapeutic potential of bioelectronic scaffolds and piezoelectric biomaterials. As a result of these smart systems, bone regeneration can be actively controlled by responding to external or internal biophysical cues, including electrical and mechanical stimulation. A critical examination of recent in vivo studies using piezoelectric ceramics and polymers is presented in this review which explores the role of endogenous bioelectric signaling in bone healing. Furthermore, this study assesses the interaction between conductive scaffolds, electrical stimulation modes, and piezo-responsive materials to improve osteogenesis, osteointegration, and vascularization. A particular emphasis is placed on translational implications, scaffold fabrication techniques such as 3D printing, and the integration of remote-controlled stimulation systems for battery-free and self-sufficient stimulation. The insights provided here provide a roadmap for developing next-generation bioelectronic platforms that overcome current clinical limitations in orthopedic repair.

Keywords: Bone tissue engineering, electrical stimulation, bioelectronic scaffolds, piezoelectric biomaterials, in vivo regeneration, smart biomaterials, osteogenesis.

1. Introduction

Bones play a crucial role in physical activity and organ protection. Small bone injuries often heal owing to bone's natural ability to repair tissues. However, larger defected bones continue to present a challenge to clinicians [1]. In traditional bone grafting techniques, such as autografts and allografts, complications may occur such as donor site morbidity, a limited supply, immune response, and potential transmission of diseases [2, 3]. It has been possible to repair large bone defects caused by surgical resections, congenital malformations, and trauma by applying bone tissue engineering (BTE) applications and regenerative strategies [4]. As a result, the field of bone tissue engineering (BTE) has emerged as a solution that uses biomaterials, cells, as well as bioactive molecules to promote the regeneration of bone tissue [5]. BTE approaches are evolving, including in vivo tissue engineering, which uses the body as a natural bioreactor and eliminates the need to manipulate cells ex vivo. This approach also promotes host-mediated regeneration [6].

As part of the osteointegration process of implanted devices, stimulation is an essential component. A number of osteoinductive growth factors have already been incorporated into bone scaffolds, including bone morphogenic proteins and transforming Growth Factors, to accelerate bone mineralization and cell proliferation [7]. In light of the prevalence of diseases such as bone fracture, bone cancer, and osteoporosis worldwide, there is an increasing demand for biomaterials for bone repair or replacement [8]. In recent years, bioelectronic technologies have made it possible to directly interact with biological tissues through implantable devices that can deliver precise electrical stimulation while simultaneously detecting physiological parameters [9, 10]. Physiological processes within cells are governed by the endogenous physiological field. Changes in the exogenous electric and magnetic fields affect the arrangement, migration, proliferation, and differentiation of osteoblasts [11]. As a result of the electrical signal's stimulation of bone cells, surface membrane proteins are activated, as are $Ca2^{+}$ voltage-gated channels on the cell membrane surface. Consequently, the intracellular and extracellular $Ca2^{+}$ concentrations are altered by this process. It has been found that direct current (DC) stimulation induces the release of prostaglandin E2 (PGE2), growth factors and morphological substances, which influence cellular functions [12]. As a result of recent advances in tissue engineering, new strategies have been developed that combine robust materials with smart systems capable of responding to external stimuli in order to enhance osseointegration and repair. In order to accelerate bone repair/healing, ex-situ stimulation techniques such as ultrasound, electromagnetic and electrical stimulation are often used. There are several techniques for improving bone healing, including electrical stimulation, which stimulates proliferation and proliferation [13]. Smart biomaterials are defined as those that stimulate or induce tissues in response to internal or external stimuli. In addition to detecting and responding rapidly to disease environments and exerting therapeutic effects while maintaining physiologically healthy tissues, smart stimuli-responsive biomaterials are capable of maximizing therapeutic efficacy and reducing undesirable side effects, improving patient quality of life [14,15]. Smart stimuli-responsive biomaterials represent a significant advancement over conventional biomaterials due to their ability to react dynamically to both internal and external stimuli. Over the past few years, these innovative materials have attracted growing attention from the scientific community, particularly in the field of bone tissue engineering. Furthermore, these materials often integrate multiple therapeutic strategies to enhance overall treatment efficacy through synergistic mechanisms. The objective of this review is to evaluate in vivo characterizations of bone tissue's bioelectrical properties comprehensively, with a specific focus on how these properties are altered in disease models. This study seeks to highlight the role of endogenous bioelectrical signaling in bone healing and remodeling by systematically evaluating animal experiments that mimic human bone pathologies. This review also discusses the potential for bioelectrically-informed therapeutic strategies to mimic healthy bone environments. Finally, this synthesis provides insights into the translational potential of in vivo bioelectrical research for advancing orthopedic and bone tissue engineering interventions.

2. The role of biophysical cues in bone healing

In orthopedics, bone grafting is one of the most common medical procedures used to increase bone regeneration. However, bone grafting has a variety of limitations and risks for patients. Therefore, artificial bone and substitutes that do not harm healthy tissue, do not present bacterial or viral risks to patients, and can be used at any time, in any amount, are preferred [16]. During bone tissue injury, there is a decrease in electrical potential at the location of the defect. Fortunately, the development of periosteum-like tissues frequently restores the local electrophysiological microenvironment at the defect site for small lesions that are below a critical size threshold. Thus, restoring electrophysiological conditions by growing periosteal tissue attracts endogenous cells around the defect site via galvanostatic interactions. Ionic charge interactions can act as recruitment mechanisms by enhancing protein adsorption and cell adhesion [17]. Because bone's bioelectrical properties control tissue homeostasis and repair, it is important to understand how bone tissue electrophysiology is affected after an injury. Under normal physiological conditions, bone tissue is electronegative. However, when fractured or injured, bone tissue becomes more electronegative [18-19]. By increasing Flow of ionic current to the point of damage, MSCs and osteoblasts are able to migrate more readily, nutrients and growth factors are able to reach the site, and other biological processes are able to carry out. According to in vitro studies, a negatively charged surface attracts cations, such as $Ca2^{+}$, present within biological fluids, which then enhances cellular adhesion by promoting protein adsorption [20,21]. A direct electrical stimulation (DC) procedure requires the installation of a bone electrode as part of an invasive procedure. A powerful electric current is used to reduce oxygen concentration, increase pH, and hydrogen peroxide at the fracture site. Furthermore, direct current increases collagen and proteoglycans. When hydrogen peroxide is released, macrophages release vascular endothelial growth factor (VEGF), which affects osteogenesis [22]. In contrast, capacitive coupling involves placing using alternating current and two electrodes on either end of the injury to cause the fracture to repair itself.

In response to the proliferation of osteoclasts, calcium concentrations increase intracellularly as they are transferred into the cell. According to many studies, calcium ions are translocated through calcium channels, as a result of capacitive coupling, prostaglandins and calmodulin are increased. [23]. It is suggested by [24] that in addition to evaluating osteogenic and electrophysiological properties of osteoblasts, additional investigations into the exhibited regenerative properties may be of interest. It has been demonstrated that the mechanical characteristics of wounds and surrounding tissues differ from each other when wound cells secrete ECM and soluble compounds.

3. Design and Fabrication of Bioelectronic Scaffolds

Tissue engineering is currently experimenting with alternative scaffold materials to conventional scaffold materials to treat bone defects, caused by tumors or infection. A temporary artificial condition that promotes bone tissue growth can be created through bone tissue engineering to prevent bone disorders. The artificial environment combines engineering and biological characteristics to treat bone diseases [25]. There has been significant research on the piezoelectric properties of bones. They generate electrical potentials when mechanically deformed and generate mechanical stress when electrically stimulated. In recent years, tissue regeneration efforts have greatly benefited from the development and availability of tailored 3D scaffolds. Scaffolds prepared by fused deposition modeling (FDM) 3D printing techniques are both readily available and of high utility [26]. Bone tissue naturally exhibits piezoelectric properties, but they have not been examined systematically within scaffold guided strategies. Conductive materials include ceramics, metals, and polymers, which have numerous advantages. In addition to geometric freedom, biological relevance, and mechanical strength, conducted scaffolds offer additional biophysical and biochemical cues that contribute to bone regeneration [27]. In healthy bone, signaling pathways are controlled by cells and extracellular matrix, and they are communicated via electrical synapses. It is possible to repair damaged bone tissue with electrical stimulation (ES) and conductive scaffolding. As a result, "smart" biomaterials that can provide electrical cues directly to cells are becoming increasingly important in bone tissue engineering [28]. In order to produce scaffolds with enhanced electrical properties, a variety of conductive materials, particularly conductive polymers, have been investigated. As well as possessing electrical and magnetic properties, these organic materials also possess flexibility and ease of processing, combining the electroconductivity of metals and semiconductors with the flexibility and ease of processing common to polymers. A number of conductive polymers are currently being explored for scaffold fabrication, including polyaniline (PANI), poly(3,4-ethylenedioxythiophene) (PEDOT) and polypyrrole (PPy) [29,30]. When combining tissue engineering techniques with the concept of enhancing bone healing through electrical stimulation, it is necessary to adjust the electrical properties of the scaffolds. The electrical conductivity of scaffolds can play an important role in delivering electrical stimuli locally to the patient. The scaffolds were made more conductive by using compositions of biocompatible conductive polymers. In addition to mediating electrical stimulation, conductive polymers can stimulate bone regeneration, as well as improving scaffold mechanical strength, biodegradability, and in vitro biocompatibility. Previous studies demonstrate that conductive polymers have the ability to improve scaffold mechanical strength, biodegradability, and biocompatibility in vitro [31]. For tissue engineering scaffolds, 3D printing facilitates native cellular behavior. The first step in integrating new technology, such as stimulating or monitoring cellular activity beyond biophysical and biochemical cues, is to build scaffolds that possess functional properties like electronic conductivity. Although these bioelectronic scaffolds have been widely underdeveloped, electrically conducting materials are extremely stiff. They may adversely affect desired cell behavior due to stiffness values being outside the physiological range. As a result, 3D printed scaffolds based on poly(3,4-ehylenedioxythiophene), poly (styrene sulfonate) hydrogels were proposed [32]. Studies have demonstrated that pulsed electrical signals controlled by the sympathetic nervous system and regulated by respiratory control can significantly reduce the inertia involved with standard electrical stimulation. The new treatment approach is appropriate to bone-related diseases since it focuses on electrically responsive bone tissue. A further limitation of bionic bioelectronic systems clinical application is that their biological mechanisms are not fully understood for bone defect healing. In the future, further research is required to explore these mechanisms and improve system design and material in order to increase their effectiveness and reliability [33]. In spite of the difficulty in replicating bone's natural structure, recent technological advancements have enabled the development of bone scaffolds that stimulate both local biological functions and systematic biological functions in vivo. Scaffolds must be composed of biomaterials, contain porosities that facilitate vascularization, and be capable of introducing and maintaining growth factors [34]. Thus, bone defects continue to present a significant clinical challenge, often resulting from trauma, tumors, or infection. Tissue engineering provides a promising solution through the integration of smart biomaterials and conductive scaffolds. As a result of bone's inherent piezoelectric properties, electrically stimulating scaffolds have been developed. As a result of improved conductivity, biocompatibility, and mechanical strength, conducting polymers such as PANI, PEDOT, and PPy enhance scaffold functionality. Fused deposition modeling (FDM) facilitates the fabrication of such scaffolds precisely. By delivering localized electrical cues, these advanced materials promote bone cell signaling and regeneration. However, even though conductive materials have potential, some mechanical stiffness can interfere with cell behavior. Bioelectronic scaffolds must therefore balance conductivity with physiological flexibility. It is necessary to continue research to optimize materials and understand bioelectronic mechanisms in bone repair so that innovations such as responsive electrical signaling can overcome tissue stimulation limitations. It can be concluded from the previous description that bioelectronic scaffolds can be designed and manufactured as illustrated in **Figure 1**.

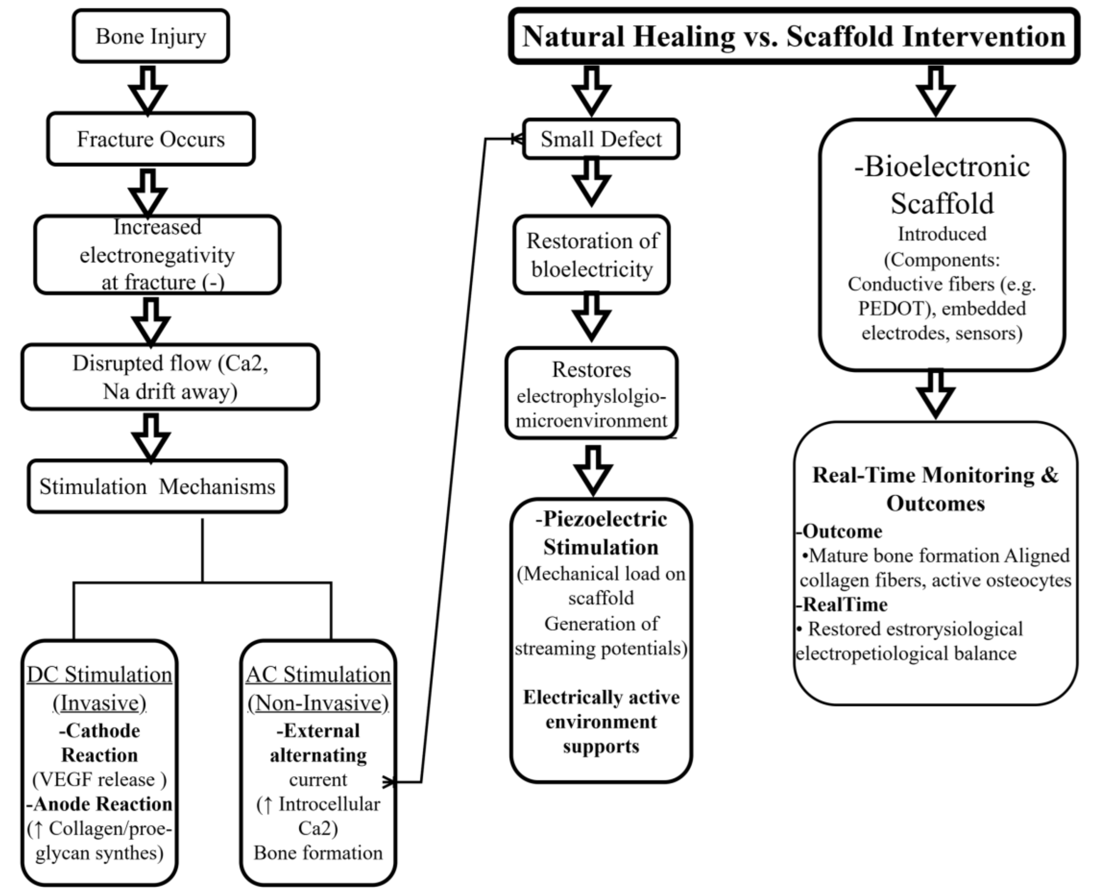

Fig. (1). Bioelectronic Scaffolds for Smart Bone Regeneration

4. Advances in Osteocyte Healing Mediated by Electrical Stimulation: Evidence and Clinical Implications

Extracellular matrixes provide information on the biophysical requirements of connective tissue cells and whether they are sufficiently equipped. Aside from responding to electric and electromagnetic fields, muscles, ligaments, bones, and cartilage also act as biophysical agents. Electric and electromagnetic fields accelerate tissue repair by upregulating growth factor mRNA levels and protein synthesis in many laboratories [35]. As a result of electrical bone stimulation, delayed unions and non-unions can be treated, especially in long bones such as the tibia. Although implantable direct current (DC) devices have not been proven to be superior to noninvasive methods like capacitive coupling (CC) or pulsed electromagnetic fields (PEMF), they may be beneficial for particular cases of nonunion with multiple risk factors. Electrical stimulation may be helpful during foot and ankle arthrodesis, but current evidence does not support its routine use in primary procedures. Ultimately, more high-quality clinical trials may be necessary in order to validate its use in a wide range of settings [36]. Furthermore, electrical stimulation has the potential to stimulate osteogenesis by activating the periosteum and attracting it to the negative electrode as a positively charged protein derived from bone and dentine. Among the effects on cell membranes are altered resting potentials and ionic distributions, which are capable of stimulating mitosis and mesenchymal differentiation. Local nerve stimulation may enhance fracture potentials, thus improving fracture repair. Furthermore, electrical currents may cause pH changes that favor osteoblasts and osteoclasts, although this mechanism is less well established [37]. It is imperative to note that electric and electromagnetic field therapies for delayed union and nonunion fractures are generally divided into four types: direct current (DC), pulsed electromagnetic fields (PEMF), combined magnetic fields (CMFs), and capacitive coupling (CC). Each of these types of therapy has a distinct clinical application. The DC stimulation technique involves surgically implanted electrodes, resulting in constant and localized stimulation, but with risks such as infection, lead breakage, and discomfort. Noninvasive PEMF mimics endogenous bone electric fields with external coils, but compliance is the key. By generating oscillating electric fields through surface electrodes, CC stimulation avoids surgery, but is continuous, reducing compliance and causing skin irritation [38]. A study [39] presented a robust and scalable approach for fabricating electroconductive 3D scaffolds made of 3D-extruded poly(ε-caprolactone) (PCL), subjected to alkaline treatment, and of poly(3,4-ethylenedioxythiophene): poly(styrene sulfonate) for bone tissue engineering under electrical stimulation. This scaffold exhibits uniform electric field distribution and has potential for clinical applications in bone grafts or bioelectronics. Using electrical stimulation, human bone marrow-derived mesenchymal stem/stromal cells (hBM-MSCs) were differentiated osteo-genetically. As well as their potential for future clinical applications, these scaffolds also hold promise for the manufacturing of bone tissue engineering grafts that are more mature and functional. Also, the study [40] examined biphasic electrical stimulation of human osteoblastic cells cultured on either dielectric bioactive grafts or composites containing conductive CNTs. As a result of conductive scaffolds, electric fields were better localized and medium conductivity was increased, resulting in greater stimulation efficiency. As a result of short-term daily stimulation with CNT/HA/Glass composites, cellular functions were significantly improved, with up to 130% increased metabolic activity, 60% increased DNA content, and enhanced expression of osteogenic genes (Runx2, OC, ALP). Using electrically conductive bone grafts, we demonstrate the ability to stimulate osteoblasts spatially and temporally, which supports future applications in non-invasive clinical electrotherapy. Furthermore, the study [41] demonstrated that electrical stimulation (ES) stimulates the production of calcitonin gene-related peptide (CGRP) by activating $Ca2^{+}$/CaMKII/CREB signaling pathways and action potentials, respectively. In both DRGs and fracture callus, ES delivered within two weeks of fracture increases CGRP expression. In addition, CGRP has been identified as indispensable for type-H vessel formation, an angiogenic and osteogenic process that contributes to osteoporotic fracture healing when ES is administered. According to the study [42], direct current electrical stimulation significantly improves the healing rate and strength of the posterolateral lumbar fusion model. In addition, this effect appears to be enhanced when the stimulation current is increased from 20 mA to 60 mA.

As a summary the role of electrical stimulation (ES) in enhancing bone regeneration has been supported by growing in vitro and preclinical evidence. There are a variety of ES modalities, including direct current, pulsed electromagnetic fields, capacitive coupling, and combined magnetic fields, that exert biophysical effects on musculoskeletal tissues by stimulating extracellular matrix (ECM) protein synthesis and growth factor production. In contrast to implanted DC devices, noninvasive devices such as PEMFs and CC provide clinical advantages with fewer complications, although patient compliance is a concern. As well as periosteal activation, altered membrane potentials, ionic modulation, and pH-dependent effects on osteoblasts and osteoclasts, ES mediates osteogenesis through multiple mechanisms. By conducting in vivo studies, scaffold integration, vascularization, immune responses, and long-term functionality will be assessed. In addition, ES evaluation under controlled in vivo conditions will provide insight into optimal stimulation parameters (e.g., waveform, duration, intensity) as well as the synergy between scaffold conductivity and endogenous bone repair mechanisms. The localized field confinement observed in conductive materials, however, is expected to minimize systemic effects and maximize osteogenic efficiency. The properties of electroconductive scaffolds make them ideal platforms for the development of noninvasive electrotherapeutic strategies to heal fractures, treat non-unions, and even develop bioelectronics for orthopedic applications. By translating their research into animal models, vital insight will be gained into their clinical viability, paving the way for customized, functional bone grafts and implantable regenerative devices. Based on the previous description, it can be concluded that advances in osteocyte healing mediated by electrical stimulation: evidence and clinical Implications can be described as illustrated in **Figure 2.**

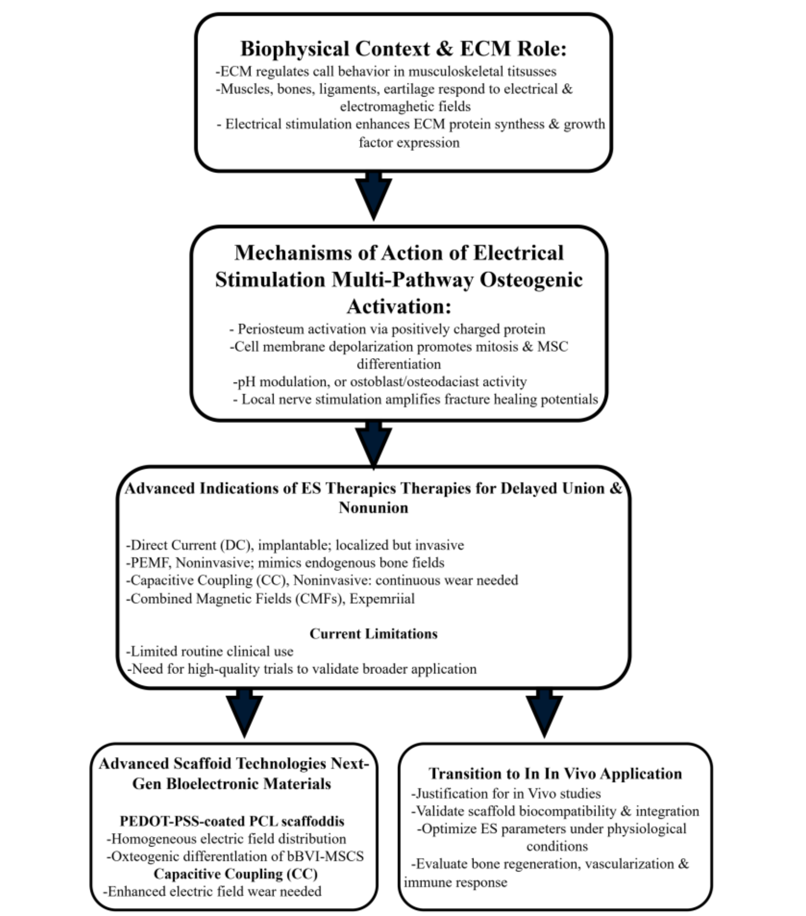

Fig. (2). Electrotherapeutic Strategies for Bone Regeneration: From Mechanisms to In Vivo Applications

4.1 An in-vivo evaluation of bioelectronic scaffolds for bone healing towards the integration of regenerative medicine

In natural bone, bioelectrical phenomena are well known for their significance in bone growth and injury restoration. As an example, piezoelectrically modulated changes in cell function promote bone tissue regeneration and repair. Several recent studies have been critically examined in recent years to demonstrate how piezoelectric biomaterials may be synergistically modulated in vivo by polarization of surface charges or stimulation by electric fields combined with their physiological features. Discuss piezoelectric bioceramics (such as magnesium silicate and barium titanate) and biopolymers such as collagen and polyvinylidene fluoride (PVDF) [43].

Biomaterials need to be studied in vivo to determine tissue compatibility. Chemical structure, toxicological, electrical, physical, mechanical, and morphological properties of the materials, along with the degree, nature, and extent to which they are exposed, must be understood. In an in vivo experiment, a predetermined shape is placed within the bone of a mammal (rat, rabbit and mouse). The main objective of testing the tissue compatibility of a biomaterial in vivo is to determine whether the implant is safe and biocompatible in a biological environment [44]. It has been demonstrated for the past few decades that electrical stimulation can promote osseointegration both in vitro and in vivo, and a variety of approaches have been employed, ranging from various electrode configurations and conditions to varying sources of electrical current. In vivo research has been performed primarily with animal models, and human subjects have not yet been studied [45]. Also, during an in vivo study conducted by [46] on six male beagle dogs, 90 titanium dental implants of various sizes (6 mm, 9 mm and 11.5 mm) with a smooth surface were placed on the bone-implant interface around dental implants. However, after 15 days of electrical stimulation, a significantly higher bone implant interface contact area was observed for the group (20 μA) than for the groups (10 μA) and control group. Moreover, an experimental basis was provided by the research of [47] studied bone-forming properties with a piezoelectric composite membrane of barium titanate and polylactic acid (BT/PLA) to provide a basis for clinical studies relating to guided bone tissue regeneration. It stimulates bone regeneration in animals. Within 4 weeks of surgery, bone growth was evident along the defect edges, along with extensive marrow cavity formation. The defect had been essentially closed by 12 weeks, showing similar density and mineralization to normal bone tissue. In addition, a study of Barium Titanate BaTiO3/multiwalled carbon nanotubes/collagen membranes (BMCs) has been reported by Ting J. et.al [48]. These membranes possess excellent physicochemical properties, including improved surface hydrophilicity, optimal piezoelectricity, and outstanding biocompatibility, making them ideal for bone regeneration. This technique uses a biomimetic periosteum, while simultaneously utilizing ultrasound synergy to promote bone repair. In order to accomplish this, electrical conditions are improved and macrophage polarization immunomodulated.

A piezoelectric composite membrane was developed in the study [49] as a charge generator for bone regeneration from defects. Composite membranes were constructed by mixing Barium Titanate powder with electroactive copolymers (PVDF-TrFE). An analysis of the histological specimens revealed new formed bone with a high mitotic activity. It was also evident that a pronounced callus had formed at the bone-membrane interface. According to the study by Weiguang W. et.al [50], microcurrent application has a beneficial effect on osteoconductive grafts reinforced with electro-active nanoparticles, as demonstrated by different biological events at cellular and molecular levels in bone. There have been a variety of biological and morphological evaluations conducted to determine the properties of PCL/graphene scaffolds fabricated via additive manufacturing. These scaffolds contain varying concentrations of graphene. As a result of exogenous microcurrent therapy, PCL/graphene electro-active scaffolds were found to promote new tissue formation in vivo. Also, the study [51] investigated the interface between PVDF (Viilidine fluoride) and cap rats' bone tissue (both PVDF-piezoelectric and non-piezoelectric). The research findings indicate that the piezoelectric effect was a significant factor in the formation of new bone tissue inside piezoelectric tubes. That bone growth was likely caused by the electret effect or by micro deformations that occurred in the piezoelectric tubes as a result of intra-articular pressure variations during gait. The effects of poly-L-lactic acid (PLLA) films on promoting ossification were investigated by Shimono T. et.al [52] by inserting them uniaxially onto rabbit tibiae's periosteum and the film's piezoelectric properties. The newly generated osteoid was detected after 1 week, and matured over the next 6 to 8 weeks. Moreover, through the use of functionalized piezoelectric materials, the investigation [53] presented a biomimetic periosteum preparation strategy for comprehensively enhancing bone regeneration. The poly (3-hydroxybutyric Acid-CO-3-Hydrovaleric Acid) (PHBV) polymer matrix, polydopamine-mudified hydroxyapitite (pha), and barium titanate (PBT) materials were used to produce an excellent piezoelectric periosteum with improved physicochemical properties. As a result of simple one-step spin coating, these materials were incorporated into a polymer matrix, resulting in a multifunctional piezoelectric periosteum. Besides, the study [54] examined how poly (vinylidene fluoride-trifluoroethylene)/barium titanate (P(VDF-TrFE)/BT) membranes affected in vivo bone formation. The results indicated that P(VDF-TrFE)/BT is effective in promoting bone regeneration, and may be an effective substitute to guided bone regeneration. Furthermore, the Ritopa D. et.al. [55], a bone regeneration method by hybridizing electrical stimulation is employed by using a PLLA (Poly (L-lactic acid)) degradable piezoelectric nanofiber scaffold that, in conjunction with ultrasound (US), generates surface charges that promote bone reconstruction. An ultrasound-enabled biodegradable piezoelectric scaffold could have a significant impact on tissue engineering by offering an electrical stimulator that is biodegradable, battery-free, and remotely controlled.

In the study by Jalia V. et. al. [56] collagen composite scaffolds and electrical stimulation were investigated in order to find out how they affected the Wingless-related integration site pathway in critical bone repair. After the scaffolds had been grafted at the defect site, they were electrically stimulated twice a week for five minutes using 10 μA of current. The findings of this investigation demonstrate that the use of ES was able to modulate the Wingless-related integration pathways and accelerate osteogenesis. Besides, in the study by Kevin J. et.al [57] investigated the effects of osteoconductive bone graft substitutes (coralline hydroxyapatite) and osteoinductive stimuli on lumbar spinal fusion. It is possible to increase stiffness, fusion success, and ultimate load to failure in a dose-dependent manner by using DC electrical stimulation. It was observed that animals undergoing fusion with the 100 μA implantable stimulator had higher ultimate loads and stiffness than those undergoing fusion with the 40 μA implantable stimulator.

Moreover, a piezoelectric biological ceramic, hydroxyapatite, and barium titanate (HABT) implanted in the jawbones of dogs, was prepared by Feng J. et.al [58] and implanted to study stress generated potentials in osteogenesis and their mechanism. As part of the research on developing strong and tenacious artificial bones using ceramics made from hydroxyapatite (HA) and piezoelectric materials, the result indicated accelerated bone growth parallel to polarization direction on HA - $BaTiO_3$. Additionally, in order to stimulate electrically stimulated osteogenesis, Bin Yu et.al. [59] developed an electret-based bio-nanogenerator for host-coupling. The porous aligning nanofibers were fabricated using two-component dispersed coaxial electrospinning as the surface charge self-recovery electret mat for energy conversion. Following implantation, the mat was coupled with the interstitial fluid and stimulated by the host to produce a bio-nanogenerator capable of coupling to the host. A significant increase in osteogenic differentiation was observed in vitro as well as improved bone repair performance in vivo. To enhance bone regeneration, Peng Y. et.al [60] has developed a material with two parallel interspersed zones of high and low piezoelectricity, to produce microscale piezoelectric zones (MPZs). K0.5Na0.5NbO3 (KNN) ceramics are specifically laser-irradiated to produce micro-zone phase transitions, resulting in a versatile and effective laser-irradiation technique. By distributing piezoelectricity within a micro-zone, MPZs can bear bone-like electric cues. Even without seeding stem cells, MPZs promote osteogenic differentiation of stem cells in vitro and bone regrowth in vivo. In addition, the study [61] reports the synthesis of HA Nanowire-Nanosheet MgSiO3-Chitosan polymer (HA-MS-CS polymer). As well as stimulating the growth and differentiation of bone marrow-derived mesenchymal stem cells (rBMSCs), the scaffold also stimulates the expression of osteogenic differentiation-related genes and vascular endothelial growth factor (VEGF).

By using digital light processing 3D printing, piezoelectric acrylate-epoxidized soybean oil (AESO) scaffolds doped with piezoelectric Ag-TMSPM-pBT nanoparticles (AESO-ATP scaffolds) were studied by Guanlin L. et.al [62]. AESO-10ATP scaffolds can promote osteogenic differentiation of BMSCs in vitro and bone fracture repair in vivo, indicating they may be well suited to bone healing applications.

Bioelectrical properties of natural bone contribute significantly in modulating cell behavior during tissue regeneration, as piezoelectricity plays a crucial role during growth and repair. As a result of these mechanisms, recent advances have focused on developing piezoelectric biomaterials that can be used to enhance bone healing and in vivo validation. Several studies examining piezoelectric ceramics (such as barium titanate, magnesium silicate) and polymers (such as PVDF, PHBV, PLLA), individually or in combination with electrical stimulation, have been presented in this review. A number of studies using rabbits, rats, and dogs have demonstrated enhanced osseointegration, accelerated osteogenesis, and improved bone-implant interfaces by altering surface charge, stimulating microcurrents, and designing scaffolds in accordance with biomaterials. A number of engineered materials have shown promise in regenerating critical-sized defects, including barium titanate/poly (lactic acid) composites, piezoelectric PVDF-TrFE membranes, and biomimetic periosteum constructs. In addition, synergistic techniques for bone regeneration using biodegradable piezoelectric scaffolds (e.g., PLLA nanofibers) may represent a breakthrough in battery-free, remote bone regeneration. In view of the previous description, it can be concluded that an in-vivo evaluation of bioelectronic scaffolds for bone healing towards the integration of regenerative medicine can be described as shown in **Figure 3**. In Appendix, we summarize the chronology of in vivo experiments (**Table A**).

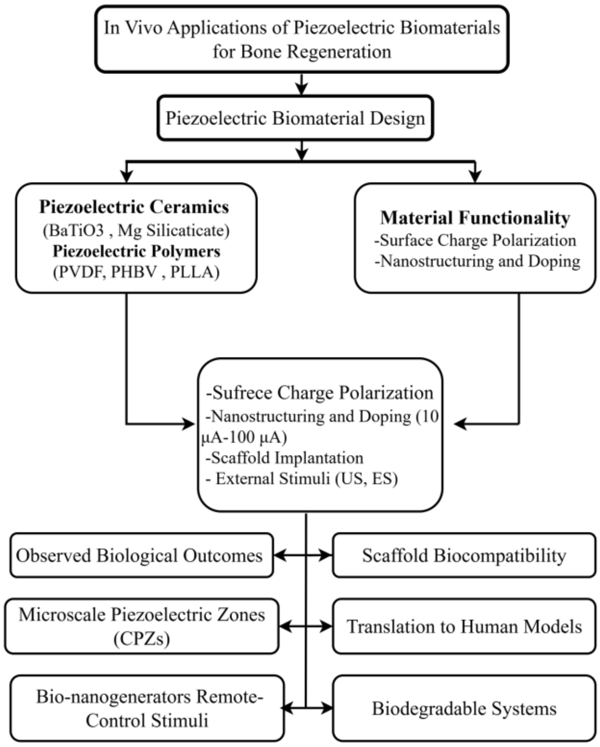

Fig. (3). In Vivo Applications of Piezoelectric Biomaterials for Bone Regeneration

5. Future Perspectives

As a result of reviewing prior research and critically evaluating the reported findings, the following future perspectives may assist future advancements in the field of bone tissue engineering

1-To optimize regenerative outcomes, it is necessary to study immunomodulatory pathways, particularly macrophage polarization and angiogenesis.

2-Development of soft, flexible bioelectronic materials that align more closely with bone mechanical properties, as well as materials that reduce immune responses.

3-In vivo stimulation protocols should be standardised to facilitate cross-comparison and optimization.

4-An integration with wireless, self-powered systems using biomechanical or ultrasound-driven nanogenerators to provide controlled, long-term stimulation without the need for external power sources.

5-To avoid overstimulation or tissue damage, stimulation parameters are precisely controlled (frequency, intensity, waveform) in patient-specific contexts.

6-Through multi-center clinical trials, it is ensured that the product is safe, biocompatible, and effective in humans.

6. Conclusion

As a result of this review, strong in vivo evidence supports the effectiveness of bioelectronic scaffolds and piezoelectric biomaterials for bone regeneration. Studies have consistently demonstrated that controlled electrical or piezoelectric stimulation enhances osteogenesis, osteointegration, and vascularization. Among the tested materials, barium titanate, P(VDF-TrFE), and PLLA demonstrated excellent biocompatibility and bone-forming ability, while conductive polymers such as PANI, PEDOT, and PPy improved scaffold conductivity and mechanical strength. By regulating cellular signaling and promoting angiogenesis, electromechanical stimulation accelerates bone repair in animal models. While most of the data are still preclinical and stimulation parameters have not been standardized, future efforts should focus on flexible, self-powered systems that mimic bone's electrical and mechanical environment. Bioelectronic and piezoelectric scaffolds have significant potential for overcoming conventional graft limitations and advancing next-generation orthopedic treatments.

Data Availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate Ethical approval was not necessary.
Competing Interests: The author reports there are no competing interest

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Table A Summary studies for in-vivo experiments

Scaffold structure	Animal model	Site of implantation	Conclusion	Ref./year	General comments
Uniaxially drawn poly-L-lactic acid (PLLA) films	Rabbit	Tibia	After insertion, new osteoid was observed at 1 week, and matured over 6 to 8 weeks following insertion of drawn polylactic acid films. Shearing stress at 45 degrees to the axis of orientation promoted the greatest amount of ossification.	52/1996	It has been observed that the introduction of piezoelectric PLLA films can promote osseointegration as a result of their piezoelectric effects, and this appears to be clinically useful.
HA-BaTiO3	Dog	jaw	As a result of histological observation, HABT was significantly more effective in growing and repairing bone than HA ceramics. Tissue growth around the HABT ceramic was direction-dependent, collagen arranged orderly and bone grew orderly. The order growth of bone enhanced the effectiveness of osteogenesis on the implanted HABT ceramic surfaces.	58/1997	A deeper understanding of the beneficial enhancement effects of piezoelectric materials as well as their mechanisms will enable the development of stronger and more resilient artificial bones using piezoelectric systems.
Coralline HA	Rabbit	Lumbar	A rabbit spinal fusion model showed that direct current electrical stimulation increased fusion rates in a dose-dependent manner. Coralline hydroxyapatite, however, is an osteoconductive material and therefore requires an osteoinductive stimulus in order to ensure a reliable fusion process.	57/1999	By combining coralline hydroxyapatite and direct current electrical stimulation, fusion rates can be increased in a rabbit spinal fusion model without harvesting bone from the iliac crest.
Barium Titanate + electroactiv e copolymers (PVDF-TrFE)	Rabbit	Tibia	Based on histological analysis, it was determined that the composites PVDF-TrFE/BT 90/10 vol% possessed high mitotic activity, which indicated their bio-activity.	49/2004	Based on the results of the study, further applications of these membranes in bone regeneration are encouraged.
PVDF [P (VDF-TrFE)] piezoelectri	Rat	Femur	The findings indicate that there was no fibrous tissue growth between PVDF tubes (piezoelectric and	51/2004	Despite the findings of this study suggesting that the piezoelectric PVDF was positive for bone formation, further research is

c			non-piezoelectric) and bone tissue at the interface formed between the PVDF tube and bone tissue. There was however trabecular arrangement within the piezoelectric tubes, which formed bone tissue.		needed to more accurately quantify that phenomenon. Also, it is essential to examine the applicability of the technique from a clinical standpoint.
Titanium	Dog	Dental	The main finding of this in vivo study can be summarized as follows: after electrical current stimulation at 20 µA applied to dental implants for 15 days, the contact area of the bone implant significantly increased.	45/ 2014	By electrically stimulating dental implants, a larger area of bone-implant interface contact can be generated due to bone formation. Different electrical current intensities and durations need to be investigated in order to clarify the potential of this methodology.
poly(vinylidene fluoride-trifluoroethylene)/barium titanate (P(VDF-TrFE)/BT)	Rat	Skull	Implanting the P(VDF-TrFE)/BT membranes in the animal model led to a greater amount of new bone formation than implanting polytetrafluoroethylene membranes, according to histomorphometry and gene expression analyses.	54/2014	It is possible that this composite could represent an effective alternative to currently employed biomaterials for the purpose of guided bone regeneration
Hydroxyapatite nanowire@ magnesium silicate nanosheets (HANW@ MS) core−shell	Rat	Skull	It has been demonstrated that the HANW@MS/CS scaffold can substantially improve the osteogenic and angiogenic differentiation of rBMSCs in vitro and facilitate the establishment of new blood vessels and bones in vivo as compared to the CS and HANWs/CS scaffolds.	61/2017	Since calcium, magnesium, silicon, and phosphorus are crucial components of bone tissue, HANW@MS core-shell porous hierarchical nanobrushes with multifunctional properties are expected to be promising in the treatment of various bone defects and in the delivery of medication.
$K_{0.5}Na_{0.5}NbO_3$ (KNN) ceramics	Rabbit	Femur	As a result of the hierarchical microscale piezoelectric zones surface, osteogenic differentiation was induced in vitro and bone regeneration was induced in vivo. In the study of stem cell behavior and tissue regeneration by controlling piezoelectric cues using microscale piezoelectric materials to mimic in vivo electrical microenvironments, it will be possible to manipulate these behaviors.	60/2017	By simulating the spatially specific piezoelectricity of bone, future research on the rational design of tissue regeneration materials will be greatly facilitated
Titanium	Dog	Tibia	The main outcome of this study can be summarized as follows: the bone implant contact area significantly increased following electrical current stimulation at 20 lA provided to dental implants for 15 days.	46/2017	According to this study, electrical stimulation of dental implants can result in a larger area of bone–implant interface contacts due to bone formation. Further research may be required to clarify the potential of this method by taking into account factors such as electrical current intensity and duration.
Barium titanate/poly lactic acid (BT/PLA)	Rat	Skull	Piezoelectric composite membranes made from BT and PLA have good osteogenic properties and provide a new approach for supporting the	47/2019	Based on the results of this study, it has been concluded that the electrical microenvironment at the repaired defect promotes bone tissue regeneration, which may serve as a new tool for treating

			development of membranes for bone tissue regeneration		guided bone tissue regeneration. Piezoelectric composite membranes are easy to prepare, inexpensive, and have potential applications in bone reconstruction and regeneration.
poly(ε-caprolactone) (PCL)/graphene scaffolds	Rat	Skull	The scaffolds produced by this method induce an acceptable level of immune response, indicating high potential for application in vivo. The scaffolds were used to treat a critical size defect in the rat calvaria with and without applying micro-electrical stimulation (10 μA).	50/2019	The results of the investigation suggest that the use of scaffolds containing graphene and electrical stimulation increases cell migration and influx, resulting in the formation of new tissue, well-organized tissue deposition, and the remodeling of bone.
biodegradable piezoelectric PLLA (Poly(L-lactic acid)) nanofiber	Mice	Skull	As shown by the in vivo results, the group using the piezoelectric scaffold and ultrasound was highly effective at promoting mineral/bone formation, ALP release, and osteoblast migration. In addition to the excellent performance of piezoelectric biodegradable PLLA nanofibers, these observations demonstrate the regenerative effect of surface charge, which can only be produced by the PLLA nanofibers when applied ultrasound.	55/2020	This study proposal is an extension of the presented work, which is primarily focused on demonstrating the significant osteogenic effect of surface charge generated by a novel biodegradable, battery-less and remote-controlled electrical stimulator of piezoelectric polyethylene nanofiber tissue scaffold.
polycaprolactone (PCL)	Rat	Femur	It is possible to efficiently convert biomechanical energy into electrical power by using host coupling bio-nanogenerator, which forms an electrical environment in the target region within the host, thereby stimulating bone regeneration through electrical stimulation. In vitro and in vivo, host coupling bio-nanogenerator was shown to powerfully activate osteogenic differentiation.	59/2021	An investigation of the host coupling effect for implantable self-powered energy conversion systems is presented as well as an exploration of tissue regeneration therapy.
Biodegradable polymer matrix, antioxidized polydopamine-modified hydroxyapatite (PHA), and barium titanate (PBT)	Rat	Cranial	In vivo experiments have shown that a biomimetic periosteum combined with endogenous piezoelectric activation synergistically accelerates new bone growth in a critical-sized cranial defect model in rats. After 8 weeks of treatment, the entire defect had almost completely been covered by new bone, with a thickness similar to that of the host bone.	53/2023	In combination, the biomimetic periosteum developed here provides favorable immunomodulatory and osteogenic properties, which suggest a method for rapidly regenerating bone tissue by applying piezoelectric stimulation.
HA/TCP	Rat	Skull	According to the results presented in this paper, composite scaffolds made up of PCL, HA, and TCP with and without the application of electrical stimulation resulted in improved bone repair and greater stimulation of the expression of bone markers and Wingless-related integration site genes, particularly during the early experimental period (30 days).	56/2023	In the initial stages (30 days) of bone maturation, electrical stimulation facilitated rapid angiogenesis and positively influenced expression of bone markers. Greater and faster mineralization of tissue is influenced by the Wingless-related integration site pathway.
Epoxidized soybean oil (AESO) + Piezoelectric Ag-TMSPM-	Rat	Skull	By combining conductive Ag nanoparticles with Ag-TMSPM-pBT nanoparticles, Ag-TMSPM-p BT nanoparticles are capable of	62/2023	Based on the results of the study, 3D-printed AESO-10ATP piezoelectric scaffolds with shape memory function could be used to regenerate bone defects.

pBT (ATP)			improving the piezoelectric properties of AESO scaffolds. AESO scaffolds containing 10 weight percent Ag-TMSPM-pBT nanoparticles exhibit promising piezoelectric properties, with a piezoelectric coefficient (d33) close to that of bone tissue.		
BaTiO3/multi walled carbon nanotubes/collagen membranes (BMCs)	Mice	Skull	An animal model of a mouse cranial defect showed that electrical signals generated by wireless transmissions, as well as mechanical signals generated by low-intensity pulsed ultrasound, were transferred to macrophages, resulting in $Ca2^{+}$ influx through Piezo1 channels.	48/2024	This study introduces an innovative co-engineering technique for bone regeneration by incorporating a biomimetic periosteum with ultrasound to improve the electrical environment and modulate macrophage polarization.