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Review paper

Lead-free piezoelectric ceramics – An electroactive material that provides electrical stimulation cues for bone regeneration

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Abstract

Experimental evidence shows that natural bone is piezoelectric, and bioelectric phenomena in natural bone play an essential role in bone development and bone defect repair. Piezoelectric ceramics can deform with physiological movements and consequently deliver electrical stimulation to cells or damaged tissue without the need for an external power source. They exhibit piezoelectricity and good biological properties similar to those of natural bone and have shown great potential in bone tissue engineering. This study aims to present an overview of the relationship between electrical stimulation and bone repair as well as the principle of the piezoelectric effect, emphasizing the material characteristics, research progress and application of piezoelectric ceramics in bone tissue regeneration. The limitations of piezoelectric ceramics in promoting osteogenesis by electrical stimulation were also analysed. Overall, this review comprehensively emphasized the essential characteristics of piezoelectric ceramics and pointed out the new direction for the future development of piezoelectric ceramics.

Keywords: *bone tissue engineering, piezoelectric ceramics, electrical stimulation, piezoelectric properties*

I. Introduction

Tissue repair needs to be in a suitable microenvironment and an electrical microenvironment is crucial for bone tissue repair. As an electroactive biomaterial, piezoelectric material can generate electrical signals in response to mechanical stimulation without an external power supply, exhibiting a piezoelectric effect similar to that of a natural bone [1]. The electrical stimulation generated by piezoelectric materials can enhance the physiological electrical environment to accelerate repair; that is, the piezoelectric signal prompts cells to migrate to the damaged area and accelerate the healing of wounds [2–4]. Therefore, piezoelectric materials can be considered promising materials for bone tissue regeneration. Commonly used piezoelectric materials mainly include piezoelectric polymers and piezoelectric ceramics. Piezoelectric ceramics and their composites possess distinct properties and advantages, such as high electrical constants, good mechanical properties and good biocompatibility. As a result, they have garnered extensive attention in bone tissue engineering applications [5–8]. The properties of various types of piezoelectric ceramic composites have been explored, as depicted in Table 1. This review covers the contemporary piezoelectric ceramic materials used and their fabrication techniques and resultant properties, focusing on orthopaedic applications.

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II. Electrical stimulations: Background and association with bone

In the physiological processes of biological development, growth and tissue damage repair, signals are con-

Table 1. The properties of various types of piezoelectric ceramic composites

Piezoelectric ceramics	Composites	Content of piezoelectric ceramics	Biocompatibility	Piezoelectric properties	Mechanical properties	Ref.
$BaTiO_3$	chitosan	35 wt.%	good	d_{33} = 11.29 pC/N	-	[108]
$BaTiO_3$	PCL	10 wt.%	good	-	compression modulus increased by ~15%	[110]
$BaTiO_3$	PCL	25–65 vol.%	good	d_{33} = 1.2–2.6 pC/N	25 vol.% $BaTiO_3$ increased modulus by 35% and tensile strength by 14%	[111]
BNNT	PCLA	5 wt.%	good	-	modulus of elasticity increased by 1370%	[107]
$BaTiO_3$ NPs	PVDF	1 vol.%	good	output voltage and current increased from 1.8 to 7.0 V and 18 to 90.4 nA	tensile strength of scaffolds increased from 23.8 ± 2.4 to 27.2 ± 2.3 MPa	[112]
$BaTiO_3$	PHBV	20 wt.%	good	d_{33} = 1.4 pC/N	Young’s modulus 513 MPa ultimate force 1 N	[113]
ZnO	P (VDF-TrFE)	2 wt.%	good	-	-	[114]
ZnO	P (VDF-TrFE)	4 wt.%	cytotoxic to HUVECs, not to hMSCs	-	-	[114]
BNNT	P (VDF-TrFE)	1 wt.%	good	d_{31} = 11 ± 4 pm/V	-	[125]
$BaTiO_3$ NPs	PVDF	0.1 wt.%	-	d_{33} = 5.62 ± 2.22 pC/N	Young’s modulus 191.2 ± 0.5 MPa, tensile strength at break 13.7 ± 2.2%, tensile strain at break 660 ± 25%	[127]
$BaTiO_3$ particle	PVDF	40 vol.%	good	d_{33} = 3.9 pC/N	-	[130]
$BaTiO_3$ fibres	PVDF	50 vol.%	-	d_{33} = 61 pC/N	-	[132]
$BaTiO_3$ fibres	Ca/Mn	2/5 mol%	good	d_{33} = 3.71 pC/N	-	[133]
CMBT fibres	PLLA	20 vol.%	good	d_{33} = 3.5 pC/N	tensile strengths declined with the increases of CMBT from 43 to 2 MPa	[134]
KNN	HA	87.5 mol%	good	d_{33} = 4.2 pC/N	-	[136]
BNNT	HA	4 wt.%	good	-	modulus of elasticity increases by 120%, hardness by 129%, fracture toughness by 86%, wear resistance by 75%	[137]
$BaTiO_3$	HA	80–100 wt.%	good	d_{33} = 1.3–6.8 pC/N	compressive strength 16.2 ± 1.99–28.4 ± 3.21 MPa	[138]
$BaTiO_3$	HA	40–60 wt.%	good, 50% is the best	-	compressive strength 125-180 MPa	[139]
$BaTiO_3$	β-TCP	60 wt.%	good	d_{33} = 3.08 pC/N	-	[8]
$Ba(Zr_{0.07}Ti_{0.93})O_3$	B_2O_3	2 wt.%	good	d_{33} > 290 pC/N	-	[143]
$BaTiO_3$	$Ca_2MgSi_2O_7$	90 vol.%	good	d_{33} = 4.0 pC/N	compressive strength 19 MPa Young’s modulus 320 ± 10 MPa	[145]
nano-$BaTiO_3$	CPS	40 wt.%	good	d_{33} = 2.53 pC/N	compressive strength 13.5 ± 1.0 MPa	[146]
$BaTiO_3$	GO/PMMA	50 vol.%	good	d_{33} = 1.5 pC/N	compressive strength 75 MPa	[147]
ZnONP	CNF	15% (*w/v*)	good	-	-	[148]
$BaTiO_3$	Gel/HA	-	good	d_{33} = 14.5 pC/N	compressive strength 1.39 ± 0.03 MPa, elastic modulus 3.256 ± 0.26 MPa	[149]

stantly exchanged from tissue to tissue and cell to cell. Bioelectricity is an essential phenomenon of life activity in living organisms, and electrical signal transmission is an important way of information exchange and communication between cells, tissues and organs. The electrical stimulation enables regulation of various cellular functions, including reorganization of their cytoskeleton, differentiation, activation of intracellular pathways,

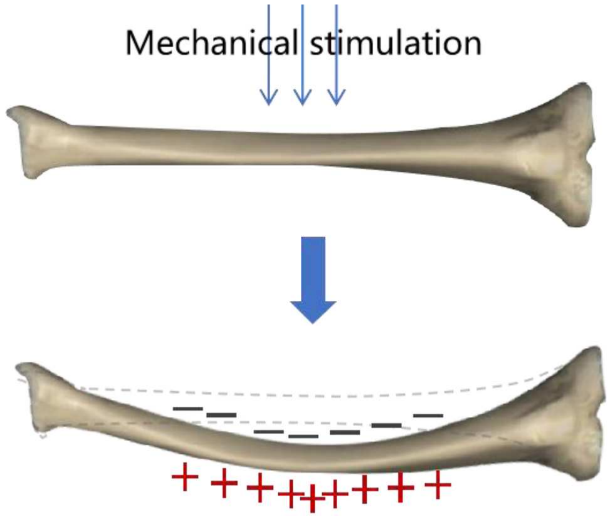

Figure 1. Piezoelectric effect of natural bone

secretion of proteins and gene expression. Piezoelectric effects occur naturally in the human body. Thus, in the 1950s, Fukada and Yasuda [9] experimentally discovered that dry bone can generate electrical signals under mechanical stress and thus proposed that bone has piezoelectric effect (Fig. 1). In bone, this behaviour was attributed to semi-conductor characteristics and to classic piezoelectric effects [10]. In the following years, other researchers also reported the presence of electric currents in bone tissue and the piezoelectric phenomenon of electrical potential generation when bone tissue is subjected to mechanical stress [11–14].

Bone tissue is composed of two components in close contact: approximately 35% organic, consisting mainly of type I collagen and a small amount of non-collagenous proteins, and approximately 65% inorganic minerals, mainly hydroxyapatite and small amounts of impurities such as fluorine and magnesium [15,16]. The results of several studies suggest that the piezoelectric effect of bone originates from the collagen component of bone tissue [16,17]. Due to the presence of piezoelectric collagen, living bone subjected to an applied mechanical stress will generate electrical signals. These bioelectric signals stimulate bone growth [18–20]. The bioelectricity inherent in bone causes electrical stimulation that contributes to bone repair, osteoporosis, bone tumors and other bone-related diseases [20–22].

The electroactive microenvironment in the bone niche is mainly due to the piezoelectric properties of bone. The correlation between the electroactive microenvironment and the ability of bone to adapt to mechanical stress and self-regenerate has led to the using of electrical stimulation (ES) as a physical cue to guide the repair of bone tissue. Although external electrical stimulation may cause side effects such as infection risk, it has been successfully used in orthopaedics because of its excellent potential for the treatment of critical bone defects and non-union fractures. Recently, it has also aroused great interest as an adjuvant therapy for bone tissue regeneration engineering. The concept of using electrical stimulation to promote fracture healing dates back to the early 19th century, including implanted power stimulation, invasive tissue stimulation (DC/pulse generator + invasive electrode) and non-invasive tissue stimulation (capacitive coupler + inductively coupled stimulation), as shown in Fig. 2. Invasive direct current stimulation is one of the widely used means of electrical stimulation therapy. Its principle is that the direct current stimulation device is directly implanted or subcutaneously placed electrode that directly applies enough DC current to stimulate bone formation [23]. Andrew *et al.* were among first to prove the therapeutic effect of inductively coupled electromagnetic fields in canine osteotomies in 1974 [24]. Non-invasive inductively coupled stimulation promotes bone formation through the use of pulsed electromagnetic field stimulation or combined with magnetic field stimulation. The study of non-invasive capacitive coupling stimulation in promoting bone tissue repair has also proved its effectiveness in promoting osteogenesis. Non-invasive capacitive coupling stimulation is the non-invasive placement of two body surface electrodes at both ends of the bone to stimulate bone formation. It is suitable to use 20–200 Hz sine wave to induce 1–100 mV/cm electric field at the repair site [23,25]. The use of electrical signals stimulation to simulate the electrical microenvironment of organisms to promote tissue

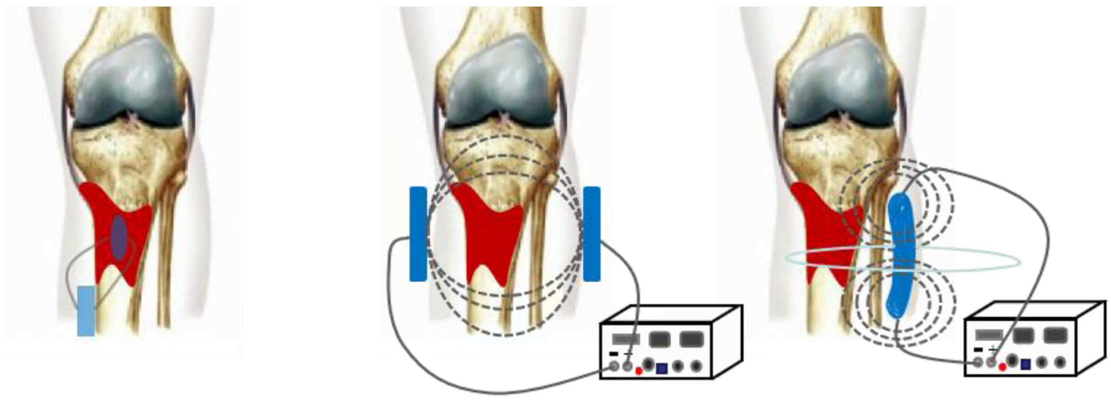

Figure 2. Implanted power stimulation (a), invasive tissue stimulation (DC/pulse generator + invasive electrode) (b) and non-invasive tissue stimulation (capacitive coupler + inductively coupled stimulation) (c)

repair and regeneration is very effective in biomedical applications [26,27]:

i) the inverse piezoelectric effect of electrical stimulation on human bone can induce microscopic mechanical deformation of bone tissue when subjected to electrical stimulation, and this mechanical stimulation is beneficial to bone healing;
ii) the promotion effect of electric current can cause cell differentiation;
iii) the biochemical changes of microcirculation around osteoblasts caused by electrical stimulation can accelerate the growth of bone;
iv) electrical stimulation accelerates the movement of calcium salts to the cathode and the deposition of calcium, which promotes the calcification of bone tissue and facilitates the formation of bone scabs;
v) electrical stimulation can activate the cyclic adenosine phosphate system in bone cells, which can be immediately followed by the activation of various enzyme systems, and the activated enzyme systems can activate osteoblasts to produce positive physiological effects (similarly, electrical stimulation activates the extracellular cyclic adenosine phosphate system, which produces hormone-like effects);
vi) electrical stimulation can also improve local blood circulation.

Mammi *et al.* [28] conducted a controlled trial with/without pulsed electromagnetic field assisted therapy in 40 cases of tibial osteotomy for degenerative knee joint disease, and showed that pulsed electromagnetic field stimulation significantly promoted fracture healing. Zamora-Navas *et al.* [29] treated 22 patients with non-healing fractures with coupling capacitors for a mean treatment time of 26 weeks, and the percentage of CT showing good fracture healing was 72.7%, and 8 patients with osteomyelitis also obtained healing, with the best healing of epiphyseal fractures. Both clinical and experimental studies of electrical stimulation to promote fracture healing have yielded relatively satisfactory results, suggesting that the effects of electrical stimulation on promoting fracture healing are positive. Although the detailed mechanism of action of electrical stimulation for bone healing is not fully understood, the extant findings adequately demonstrate its clear biological effects.

Electroactive biomaterials are a new generation of "smart" biomaterials that can deliver electrical, electrochemical, and electromechanical stimuli directly to cells [30]. Ceramic materials have received a lot of attention because of their similar composition and mechanical properties to human bone. Especially piezoelectric ceramics can exhibit piezoelectricity similar to that of natural bone. So in addition to the above-mentioned electrical stimulation therapy, the use of electroactive materials to promote osteogenesis through tissue engineering is an interesting concept to consider [31].

III. Piezoelectrics and piezoelectric effects

3.1. Piezoelectricity of materials

Materials possess piezoelectric properties due to the lack of a centre of symmetry. The deformation of such materials leads to the generation of charges of opposite polarity on opposite sides of the crystal. Fundamentally, this is due to the separation of the neutralization centres of the charges on the lattice as the material deforms along certain axes. The term applies to some polycrystals, inorganic materials and some inorganic substances [32].

The quality of the piezoelectricity from a material is characterized by the piezoelectric constant. Different boundary conditions are used to measure the piezoelectric strain coefficient (d), the piezoelectric stress coefficient (g), the piezoelectric voltage coefficient (e) and the piezoelectric stiffness coefficient (h). Among them, the most commonly used is the piezoelectric strain coefficient d_{ij}, which is expressed as the ratio of the strain change due to the change in the electric field intensity when the piezoelectric body is under constant stress; when a constant electric field is applied, the ratio of the electric displacement changes and the stress change is called the piezoelectric strain coefficient d_{ij}: The subscript i refers to the direction of the electric field,

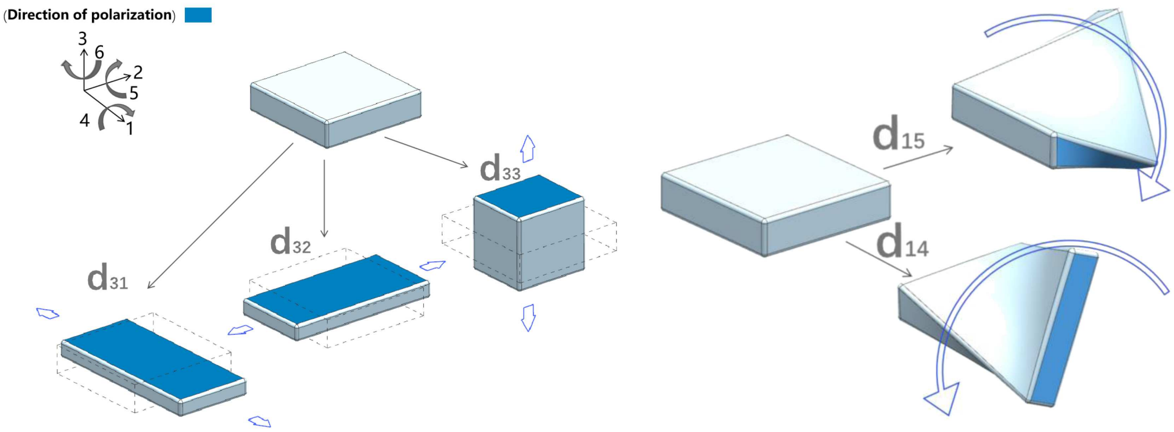

Figure 3. Schematic diagram of common piezoelectric constants (dark coloured surface represents the surface on which the charge accumulates)

$i = 1, 2, 3$. The subscript j refers to the direction of the stress or strain, $j = 1, 2, 3, 4, 5, 6$. Among them, 1, 2 and 3 indicate orthogonal axes, and 4, 5 and 6 indicate the directions of rotation around 1, 2 and 3 axes, respectively, a schematic diagram of the common piezoelectric constants are shown in Fig. 3. The calculation formula of piezoelectric strain coefficient is (unit is C/N or m/V):

$$d_{ij} = \left(\frac{\partial S_j}{\partial E_i}\right) \cdot T = \left(\frac{\partial D_i}{\partial T_j}\right) \cdot E \tag{1}$$

where D is the inductance strength, E is the electric field strength, T is the mechanical stress and S is the strain.

One of the most commonly used parameters to characterize the properties of piezoelectric materials is the piezoelectric constant d_{33}, when $i = 3$ and $j = 3$ ($i = 3$ indicates the direction of polarization, $j = 3$ indicates that the direction of applied force is along the direction of polarization, so $ij = 33$ indicates that the direction of polarization is the same as the direction of applied force during measurement). When using the piezoelectric constant to calculate the amount of charge released by the material under external force F, the following formula is used:

$$q = d_{33} \cdot F \tag{2}$$

Based on the characteristics of piezoelectric ceramics, when they are used in the construction of human electrical microenvironments, cells can be electrically stimulated without external power supply or electrode implantation, thereby promoting the formation of tissues [33].

3.2. *Piezoelectric effects*

Piezoelectric materials are materials that allow force-electric transduction. These materials can transduce the mechanical pressure acting on it to the electrical signals (called direct piezoelectric effect) and electrical signals to mechanical signals (called converse piezoelectric effect). At the macroscopic level, the piezoelectric effect can be described as the polarization of the material's interior when a piezoelectric material is subjected to an external force, i.e. a voltage appears between the two end faces, and the outer surface of the material produces opposite charges (when subjected to pressure, the direction of the electric potential on the outer surface of the material and its corresponding internal is opposite; when subjected to tension, the situation is reversed), where the voltage applied to the material leads to self-stretching or self-shrinking of the material, depending on the positive or negative direction of the voltage, as depicted in Fig. 4 [34,35].

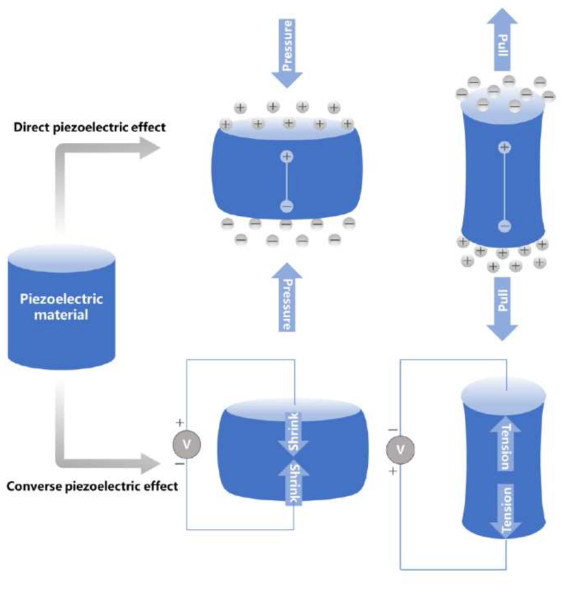

Figure 4. Power-to-electricity conversion of piezoelectric materials

IV. Application of piezoelectric ceramics in bone tissue engineering

The biological performance of materials depends on the extent to which they can simulate the microenvironment and transmit signals to stimulate cell reactions. For some piezoelectric materials this property has been proven [36–38]. Bioelectric signal, endogenous electric field and external electrical stimulation [25,39–42] play a key role in regulating cell behaviour and promoting bone repair. Piezoelectric materials can transmit these electrical signals without external stimulation equipment, and can enhance the physiological electrical environment to stimulate repair [43–46]. Thus, Zhang *et al.* [47] developed a biomechanical-energy-driven shape memory piezoelectric nanogenerator. The pulsed direct current (DC) generated from the self-powered pulsed DC stimulation device effectively promotes cell proliferation and enhances the intracellular calcium concentration (Fig. 5). Liu *et al.* [48] also demonstrated that piezoelectric $BiFeO_3$ thin films (≈10–20 nm thickness) on strontium titanate ($SrTiO_3$) implants can generate a constant built-in electropositive field and strongly interact with the electronegative potential of bone (Fig. 6). In the presence of built-in electric fields, implants with $BiFeO_3$ films with downward polarization show rapid and superior osseointegration in the rat femur.

Inorganic piezoelectric materials include piezoelectric ceramics and piezoelectric single crystals. Piezoelectric crystals, such as quartz, sphalerite and borite,

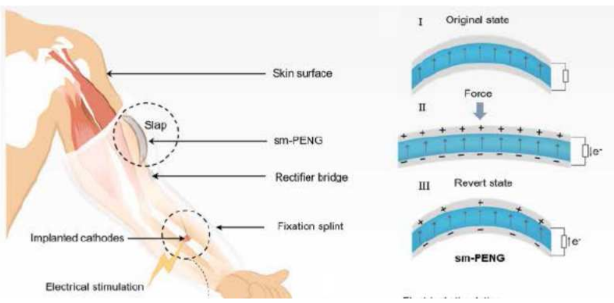

Figure 5. Schematic diagram of self-powered electrical stimulation for bone repair [47]

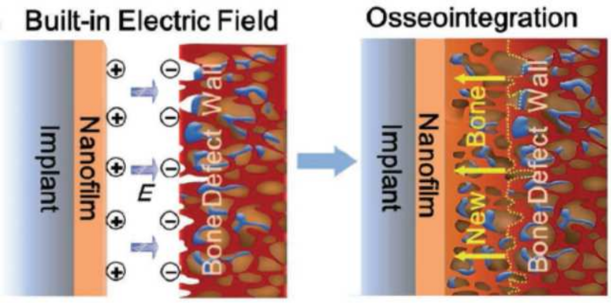

Figure 6. Illustration of rapid osseointegration between electropositive implant and electronegative bone interaction [48]

usually have high hardness, brittleness, poor piezoelectric property, low dielectric constant, limited size, but high stability. They are often used as standard frequency-controlled oscillators, high selectivity filters and high-frequency and high-temperature ultrasonic transducers [49–52]. The characteristics of piezoelectric crystals limit their development in the field of bone tissue engineering. Another kind of inorganic piezoelectric materials, such as barium titanate (BT), lead titanate, lead zirconate titanate, etc. are characterized by high hardness, brittleness and good piezoelectric properties, and can be processed into a variety of shapes. They are often used in the preparation of high-power transducers and broadband filters [53,54]. Piezoelectric ceramics are often used as a substitute for hard tissue in the field of bone tissue engineering, but not all piezoelectric ceramics can be used in biomedical field. Most industrial piezoelectric ceramics contain lead and cannot be used as biomedical materials, because even low doses of lead can cause serious health problems, such as neurotoxicity, pregnancy complications, hyperactivity disorder and slow growth in children [55,56]. Therefore, lead-free piezoelectric ceramics have become a research hotspot in the biomedical field in recent years. Among the commonly used lead-free piezoelectric ceramics are BT, alkali metal niobate-based piezoelectric ceramics ($Li_xNa_yK_{1-x-y}NbO_3$, LNKN), sodium bismuth titanate-based piezoelectric ceramics ($Bi_{0.5}Na_{0.5}TiO_3$), zinc oxide (ZnO) and boron nitride (BN). They all have high piezoelectric constants, among which BT, BN, alkali metal niobate-based lead-free piezoelectric ceramics and ZnO also have excellent biocompatibility [57]. The porosity and hardness of ceramics may support tissue integration at the interface between tissue and a porous ceramic scaffold implant [58,59], and according to different uses, piezoelectric ceramics can be processed into nanoparticles, films, coatings and so on, which is very flexible in the field of bone tissue engineering. Representative parameters such as piezoelectric material types, piezoelectric constants and key findings, as well as the results of *in vitro* and *in vivo* studies of piezoelectric materials, are clearly summarized in Tables 2–6 to facilitate comparison.

4.1. Barium titanate ($BaTiO_3$)

$BaTiO_3$ (BT) is a piezoelectric ceramic material widely used in tissue engineering. It belongs to per-

Table 2. Some representative information about the advantages and disadvantages of $BaTiO_3$-based ceramics summarized from the literature data

$BaTiO_3$ d_{33} = 191 pC/N (typical value)			
Material type	*In vitro*/*in vivo* study	Key findings	Ref.
$BaTiO_3$	dogs, *in vivo* analysis	good biocompatibility of $BaTiO_3$; both piezoelectric $BaTiO_3$ implants and electrically neutral $BaTiO_3$ implants formed good combination with bone tissue	[22]
TiO_2-$BaTiO_3$ (coating)	SD rat osteoblasts, *in vitro* study	number of cells on the surface of $tTiO_2$-$BaTiO_3$ polarized sample gradually increases; after immersing in SBF negative charges are generated on the surface, which can attract Ca^{2+} ions and promote apatite deposition.	[62]
BCZT	HOB and HUVEC, *in vitro* study	low cytotoxicity, enhanced cell viability and proliferation on BCZT ceramics was observed in compared to a polystyrene control group	[63]
PCL/ $BaTiO_3$	SaOS-2, *in vitro* study	composite scaffold has good piezoelectricity and its bioactive surface promotes the adhesion and proliferation of SaOS-2 osteoblasts	[110]
PCL/ $BaTiO_3$	MC3T3, *in vitro* study	piezoelectric response of PCL-BT (65 vol.%) specimen was 2.6 pC/N and cell growth kinetics was the best due to the increased $BaTiO_3$ content leading to enhanced proliferation and differentiation of proosteoblasts	[111]
PVDF/ $BaTiO_3$	MG-63, *in vitro* study	β-phase fraction of PVDF/$BaTiO_3$ scaffold increased by 11%, resulting in an increased output voltage by 356%; the enhanced electric cues could promote the cell adhesion, proliferation and differentiation more efficiently	[132]
PLLA/ CMBT	BMSCs, *in vitro* study	the PLLA/CMBT membranes demonstrated the strongest promotion on mineralization and osteogenic differentiation as well as the most efficient capacity against S. aureus, with PLLA and PCL/CMBT membranes as references	[134]
HA/ $BaTiO_3$	osteoblasts, *in vitro* study	the best biocompatibility and bone-inducing activity were demonstrated by the 10% HA/90% $BaTiO_3$ piezoelectric ceramics	[138]

Table 3. Some representative information about the advantages and disadvantages of LNKN-based ceramics summarized from the literature data

LNKN d_{33} = 98 pC/N (typical value)			
Material type	*In vitro*/*in vivo* study	Key findings	Ref.
PMMA/ LNKN	SD rat osteoblasts, *in vitro* study	LNKN piezoelectric ceramics have good promotion effect on cell adhesion, proliferation and activity	[70]
LNKN	SD rat osteoblasts, *in vitro* study	prepared porous LKNK samples by CIP method have higher density, better uniformity and higher piezoelectric constant; adhesion and differentiation of osteoblasts on porous materials have shown good cell compatibility	[72]
KNN	cytotoxicity test, *in vitro* study	lithium oxide solves the problem of poor KNN sinterability, but Li-KNN has a slight cytotoxicity (it is more toxic than KNN), which may be caused by the dissolution of lithium ions	[81]
KNN	SaOS-2, *in vitro* study	HA-NKN-HA composite scaffold accelerates the proliferation and differentiation of SaOS2	[135]
KNN	New Zealand White Rabbit, *in vivo* analysis	large amount of new bone tissue grows on the polarized potassium sodium niobate scaffold, and the polarized potassium sodium niobate piezoelectric scaffold can significantly induce bone regeneration	[82, 83]

Table 4. Some representative information about the advantages and disadvantages of $MgSiO_3$-based ceramics summarized from the literature data

$MgSiO_3$ d_{31} = 1.74 pC/N d_{33} = 346.7 pC/N (typical values)			
Material type	*In vitro*/*in vivo* study	Key findings	Ref.
Ti_6Al_4V-$MgSiO_3$ (coating)	BMSCs/RAW 264.7/osteoclasts, *in vitro* study; White Rabbit *in vivo* analysis	promote proliferation and differentiation of osteoblasts and inhibit osteoclasts, and induce immune regulation that is more conducive to osseointegration; coating is well combined with the host bone tissue, with higher biomechanical strength and higher rate of new bone formation	[87]
$MgSiO_3$	MG-63, *in vitro* study	scaffold can form apatite in SBF and the loaded MTZ can attack germs improving antibacterial behaviour; Mg^{2+} and Si^{4+} ions can promote the proliferation of MG-63 cells.	[88]

Table 5. Some representative information about the advantages and disadvantages of ZnO-based ceramics summarized from the literature data

ZnO d_{33} = 12.4 pC/N (typical values)			
Material type	*In vitro*/*in vivo* study	Key findings	Ref.
ZnO/TiO_2 (coating)	MC3T3-E1, *in vitro* study	cytocompatibility and osteogenic ability of MC3T3-E1 were significantly improved	[96]
ZnO (coating)	SD rat osteoblasts, *in vitro* study	piezoelectric effect of ZnO excited by low-frequency pulsed ultrasound promotes the proliferation and differentiation of osteoblasts	[97]
ZnO (nanosheets)	SaOS-2/ Macrophages, *in vitro* study	ZnO generates electrical signals under the action of the inherent mechanical force to stimulate metabolism of SAOS-2 cells and macrophages; the electrical signal activates the opening of calcium channels on the cell plasma membrane and the influx of Ca^{2+} ions, thus amount of Ca^{2+} ions in the cell increases, which makes the cell grow faster	[99]
ZnONP-CNF	MG-63, *in vitro* study	MG-63 cells could attach and spread well on the surface of all nanocomposites	[147]
P(VDF-TrFE)/ZnO	hMSCs and human umbilical vein endothelia, *in vitro* study	scaffolds had the best biocompatibility and ability to promote cell adhesion when the ZnO content was 2% (w/w)	[112]

Table 6. Some representative information about the advantages and disadvantages of BN-based ceramics summarized from the literature data

BN d_{31} = 31.2 pC/N d_{33} = 0.3 pC/N (typical values)			
Material type	*In vitro*/*in vivo* study	Key findings	Ref.
BNNTs	MSCs, *in vitro* study	BNNTs promote proliferation of MSCs and increase the total protein secretion of MSCs; BNNTs can increase the activity of alkaline phosphatase (ALP), the ratio of ALP/total protein and the activity of osteocalcin	[105]
P(VDF-TrFE)/(BNNTs)	SaOS-2, *in vitro* study	P(VDF-TrFE)/(1%BNNTs) piezoelectric film shows better mechanical and piezoelectric properties than pure P(VDF-TrFE); the film promotes the differentiation of SAOS-2 osteoblast-like cells	[136]
HA/BNNTs	ATCC CRL-11372, *in vitro* study	cells proliferate on the surface of bone scaffold and assist the deposition of apatite crystals by forming a collagen matrix; number of cells proliferates significantly within 1-3 days of culture	[11]
PLC/BNNTs	ATCC CRL-11372, *in vitro* study	interactions of the osteoblasts and macrophages with bare BNNTs prove them to be non-cytotoxic; PLC/BNNT composites displayed increased osteoblast cell viability as compared to the PLC matrix	[12]

ovskite structure, which is tetragonal at room temperature, the tetragonal phase changes into cubic phase when the temperature is higher than 120 °C and the tetragonal phase changes into orthorhombic phase when the temperature is around 0 °C [60]. BT is highly biocompatible with piezoelectric constants (d_{33}) of 191 pC/N [32] and it is only piezoelectric when it undergoes polarization (polarization process is shown in Fig. 7). Among piezoelectric ceramics, BT represents the most investigated lead-free piezoceramics [61]. In addition to its good biocompatibility and intrinsic capacity to sustain a charged surface, BT has shown great ability to improve bone cell adhesion and proliferation. Park *et al.* [62] evaluated the possibility of replacing the hard tissue of bone with BT piezoelectric ceramics by implanting pre- and post-polarized cylindrical BT piezoelectric ceramics into the femur of dogs and demonstrated the good biocompatibility of BT. The polarized surface of BT implants showed good adaptation to surrounding tissues with strong interfacial bonding. Particularly, the BT-derived calcium/zirconium-doped barium titanate (BCZT) is of interest because of exceptionally high piezoelectric values compared to other lead-free piezoelectric materials available today. High remanent d_{33} values of approximately 280 pC/N were obtained in the study by Poon *et al.* [63]. Cytotoxicity, cell proliferation, and cell viability studies were performed using Human Oseoblast cells (HOB) and Human Venous Endothelial cells (HUVEC). These cell studies demonstrate low cytotoxicity and enhanced cell viability and proliferation on the BCZT ceramics as compared to a polystyrene control group. The combination of good piezoelectric performance and low cytotoxicity highlights the potential of this class of materials to mimic the "piezoelectric effect" observed in natural bone, making it suitable for active, cell stimulating implants. Due to its mechanical characteristics, BT is usually not used as a matrix material alone when applied to bone repair.

Its most common application is piezoelectric coating as a metallic scaffold that provides good electrical stimulation. Tang *et al.* [64] prepared a titanium dioxide (TiO_2)-BT bioelectric coating on the surface of medical titanium alloy to theoretically explain the piezoelectric effect on the promotion of osteogenesis from the microscopic perspective of the relationship between the piezoelectric effect on ions, and to macroscopically characterize the deposition process of apatite in simulated body fluid (SBF) under the action of cyclic stress: the application of cyclic load generates a negative charge on the surface. The negative charge attracts Ca^{2+} to accumulate on the coating surface, promoting apatite deposition and increasing the calcium-

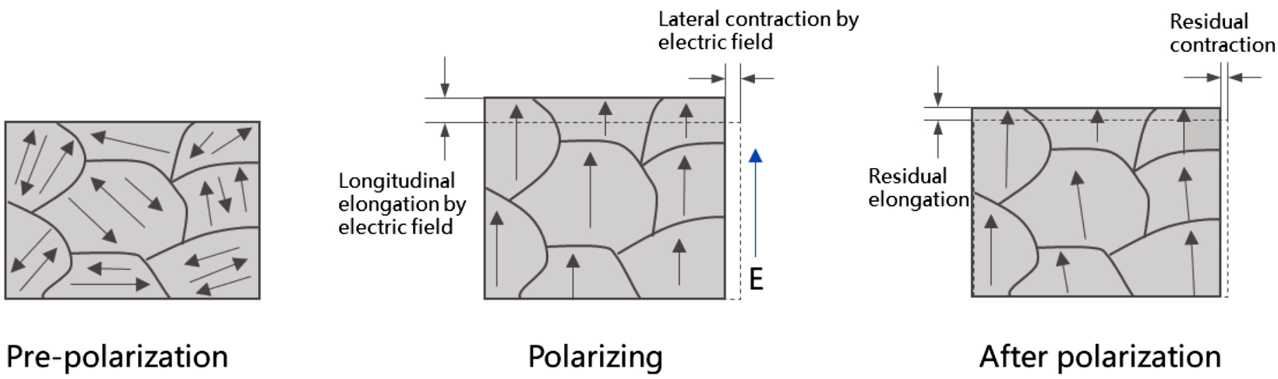

Figure 7. Schematic diagram of polarization process of BT

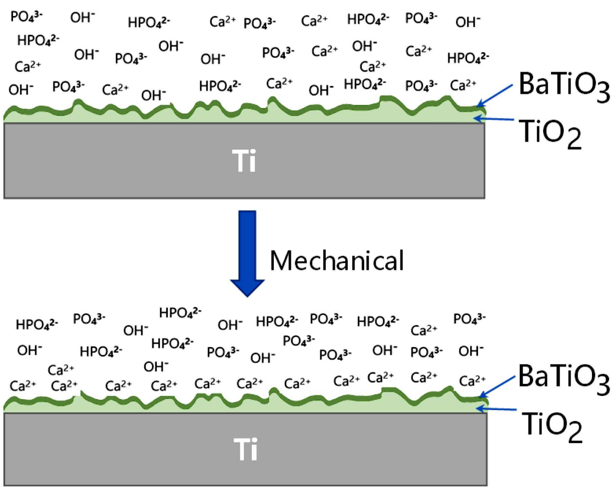

Figure 8. A periodic load is applied to generate a negative charge on the surface of BT, which can attract Ca^{2+} to gather on the coating surface

phosphorus ratio to a level close to that of human bone, as depicted in Fig. 8. Ti-6Al-4V (TC_4) is a commonly used scaffold material. In the research of Cai *et al.* [65], a BT piezoelectric ceramic coating was synthesized on the surface of a TC_4 titanium alloy, forming a BT/TC_4 material, and low-intensity pulsed ultrasound (LIPUS) was then applied as a mechanical stimulus. Electrochemical measurements indicated that LIPUS-stimulated BT/TC_4 materials could produce a microcurrent of approximately 10 µA/cm^2. *In vitro*, the greatest osteogenesis (cell adhesion, proliferation, and osteogenic differentiation) was found in mouse embryo osteoblast precursor cells (MC3T3-E1) when BT/TC_4 was stimulated using LIPUS. Wu *et al.* [66] prepared a piezoelectric BT/TC_4 scaffold by hydrothermal synthesis of a uniform BT layer on 3D printed TC_4 scaffold. The BT/TC_4 scaffolds exhibited piezoelectricity and favourable biocompatibility after polarization. Under the stimulation of LIPUS, the results of the cervical bone repair in sheep further demonstrated that the piezoelectric BT/TC_4 (poled) artificial vertebral bodies facilitated bone regeneration. Therefore, the piezoelectric BT coating with LIPUS loading synergistically promoted osteogenesis, making it a potential treatment for early-stage formation of reliable bone-implant contact.

4.2. Alkali niobate ($Li_xNa_yK_{1-x-y}NbO_3$)

Alkali niobates belong to the chalcocite structure type. In 1959, the piezoelectricity of potassium-sodium niobate ($NaNbO_3$-$KNbO_3$) binary system was studied for the first time and continued with hot-pressed $(Na_{0.5}K_{0.5})NbO_3$ ceramics having better performance. Doped $NaNbO_3$-$LiNbO_3$ has also been studied, where Nb was replaced with Ta, Sb and other elements [67–69]. In recent years, studies on the lead-free alkali metal niobates as orthopaedic implants to promote bone regeneration have gradually increased proving that they are less toxic to cells and provide a better alternative to lead-based ceramics with toxicological risks. Compared to BT, it is usually more piezoelectric and stable, expanding the range of applicability for repairing bone defectsdefects [70].

Lithium sodium potassium niobate (LNKN) was embedded in the traditional denture base material polymethylmethacrylate (PMMA), and due to the piezoelectricity of LNKN, microcurrents can be generated during masticatory movements to stimulate targeted alveolar bone growth [71]. The electrical charge on the surface of piezoelectric ceramics enhances the adhesion of osteoblasts, which subsequently affects the proliferation and differentiation of osteoblasts around the material. Miara *et al.* [72] performed theoretical and numerical study on a prototype of bone biomaterial made of a piezoelectric material periodically perforated by holes which are filled with living cells. They combined inert components with active components to build an "intelligent system", which was designed and modified to enhance the bone regeneration process. Based on the above theory, Wang *et al.* [61,73] proposed a method for homogeneous pressurized consolidation in a flexible envelope – the cold isostatic pressure (CIP) method, and used it to prepare porous LNKN ceramics. The obtained LNKN samples possess higher density, better homogeneity and higher piezoelectric constants. *In vitro* studies on the attachment and differentiation of osteoblasts on the porous material showed good cytocompatibility and the LNKN piezoelectric ceramics showed good prospects for application as bone replacement materials.

Potassium sodium niobate (KNN), like LNKN, belongs to the same group of alkali niobates and has a typical chalcogenide structure, as depicted in Fig. 9a [74], similar to potassium niobate ($KNbO_3$). The unit cell of $KNbO_3$ has an orthorhombic structure (rhombohedral phase) with a space group of *Amm*2 at room temperature, and when the temperature increases it transforms to the tetragonal phase. The orthorhombic structure is

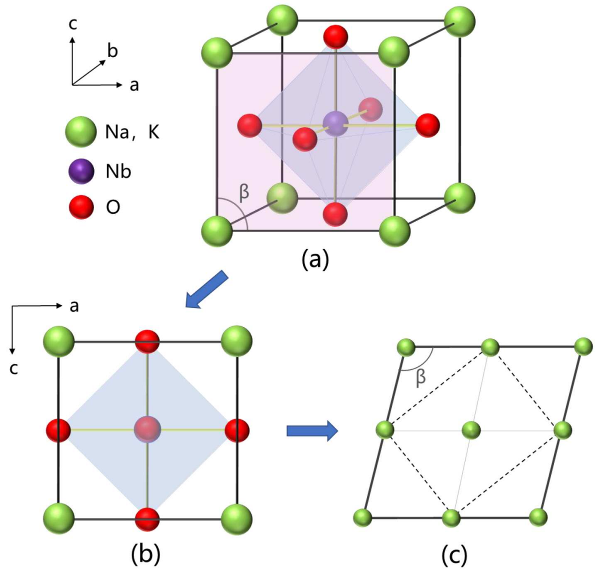

Figure 9. The unit cell structure of KNN

not a typical ABO_3 orthorhombic phase, but a monoclinic symmetric structure, i.e. the lattice parameters are $a_m = c_m > b_m$ and b_m is perpendicular to the $a_m c_m$ plane with an angle β slightly greater than 90°. As depicted in the Fig. 9b, the eight vertex positions of the unit cell are occupied by A-site ions (K^+, Na^+), the face-centred positions of the cube are occupied by six oxygen ions, and the body-centred positions are occupied by B-site ions (Nb^{5+}). In the potassium sodium niobate system, the ionization valence of A site is +1 and that of B site is +5. Fig. 9b shows the projected view of the subcell along b_m, which appears as perpendicular to c_m due to the angle β close to 90°. To show the geometry more clearly, β was enlarged to much larger than 90° and the projected views of four adjacent chalcogenide subcells were combined, but Nb and O were omitted, as depicted in Fig. 9c. Since the length of a_m is equal to c_m, the diagonal lines connected by dashed lines in Fig. 9c form a rectangle, which is the projection of the KNN cell along b_m. Thus, the chalcogenide subcell of KNN is a monoclinic crystal, and the cell has rhombohedral symmetry at room temperature. When the temperature is higher than 200 °C, the cell of KNN changes from rhombohedral to tetragonal phase and the material becomes electrically neutral. When the cell expands or contracts, the niobium-oxygen octahedron distorts, the cations in the B-site deviate from the centre of the octahedron, and spontaneous polarization occurs inside the material thus being piezoelectric. Common preparation methods of KNN include sol-gel method [75], hot pressing method [76], mechano-chemical method [77], chemical vapour deposition method [78], plasma sintering [79], etc. and the piezoelectric properties can be improved by changing the composition of the physical phase, crystal structure and ceramic densification. The piezoelectric constant of KNN is up to 416 pC/N (d_{33}), and its piezoelectric properties are comparable to lead zirconate titanate (PZT) [70].

Although BT has qualified biological response according to some studies, their temperature stability is poor and the cytotoxicity of barium and titanium ions cannot be ignored [79]. In fact, the piezoelectric properties can be improved by doping KNN with antimony (Sb), tantalum (Ta), bismuth (Bi) and other elements to replace lead zirconate titanate. Although this doped KNN has good piezoelectricity, it has little potential in the field of implantable materials due to the toxicity of the doped elements [80,81]. Undoped KNN can be used as bone repair material because of its good biocompatibility, temperature stability (high Curie temperature) and larger piezoelectric constant than natural bone. In addition, it is reported that the biocompatibility of KNN is better than that of LNKN, since LNKN has slight cytotoxicity, which may be caused by the dissolution of lithium ions [82]. Chen *et al.* [83] investigated the effect of substrate surface charge on protein adsorption and cell proliferation compared with non-polarized surfaces (NPs) and found that both positively and negatively polarized surfaces were more favourable for protein adsorption than non-polarized samples. Furthermore, cell viability staining and cell proliferation experiments were performed on porous KNN piezoelectric scaffold samples (piezoelectric constant d_{33} = 93 pC/N), which confirmed that the polarized KNN piezoelectric scaffold had good ability to induce bone-like apatite deposition while also promoting cell proliferation and differentiation. In the subsequent animal implantation model, it was also found that the KNN piezoelectric scaffold has excellent ability to induce new osteogenesis and has great potential as an electroactive material for hard tissue regeneration [84].

4.3. Magnesium silicate ($MgSiO_3$)

$MgSiO_3$ has excellent mechanical properties, chemical stability and biocompatibility. Its structure is asymmetric tetragonal perovskite structure, which determines the piezoelectric properties of $MgSiO_3$ [85]. $MgSiO_3$ also has some biodegradability and presents a rare biodegradable material in piezoelectric ceramics [86]. Magnesium (Mg) is essential in bone metabolism and a deficiency of magnesium can affect calcium absorption, negatively impacting all stages of bone metabolism, leading to slower bone growth and consequently osteoporosis and fractures. Silicon is also a trace element that affects bone growth, and $MgSiO_3$ contains both magnesium and silicon, both of which play an important role in bone growth, development, and metabolism [87].

Wu *et al.* [88] prepared $MgSiO_3$ coating on the orthopaedic implant TC_4. The coating can release Mg and Si ions, and compared to HA coatings, induced an immunomodulation more conducive for osseointegration and had high binding strength with TC_4. The bonding strength of $MgSiO_3$ coatings was 50.1 ± 3.2 MPa, more than twice that of HA coatings, at 23.5 ± 3.5 MPa. It has been proved that $MgSiO_3$ is an implantable ceramic material suitable for bone repair. Bakhsheshi-Rad *et al.* [89] prepared extremely porous clinoenstatite (CLEN) scaffolds with different pore sizes and great interconnectivity for the first time through the space holder method and subsequent sintering, and then modified them by loading antibiotic nail files (metronidazole (MTZ)) to improve the antibacterial properties of the scaffolds. The scaffolds with MTZ had an apatite-forming capability in SBF, the loaded MTZ can attack bacteria, and the release of magnesium and silicon ions can enhance the cell vitality of Human osteosarcoma cells (MG-63). The scaffold and its function are shown in the Fig. 10.

In the above studies, various forms of $MgSiO_3$ showed the function of bone repair, but these studies focused on the role of silicon and magnesium ions in regulating cell activity and promoting osteoblast proliferation and differentiation, and did not mention the piezoelectric properties of $MgSiO_3$. In fact, $MgSiO_3$ is a kind of electroactive ceramics. Hwang *et al.* [90] prepared a $MgSiO_3$ piezoelectric ceramic coating by

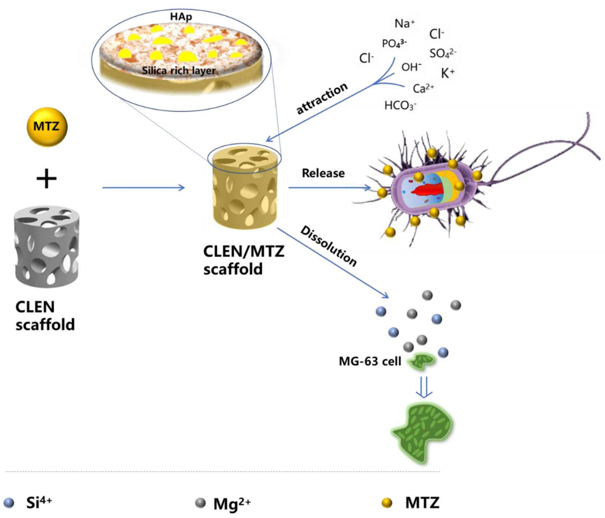

Figure 10. Schematic diagram of CLEN scaffold and its function [89]

magnetron sputtering which can be used in implantable micromechanical systems with the piezoelectric constant d_{33} = 346.7 pC/N of the coating being much higher than that of BT and common piezoelectric polymers. The current research and application of $MgSiO_3$ for piezoelectricity-promoted osteogenesis started late and there are a few data and related samples. However, piezoelectric $MgSiO_3$ has shown its advantages in constructing the electrical microenvironment for bone growth and the function of promoting osteogenesis through ion release, and it is expected to become a kind of bone repair electroactive ceramic material beyond BT.

4.4. Zinc oxide (ZnO)

ZnO has three different crystal structures, including sphalerite hexagonal structure, sodium chloride octahedral structure and wurtzite cubic structure, among which wurtzite is the most stable [91]. The lack of a centre of symmetry in wurtzite, combined with large electromechanical coupling, results in strong piezoelectric and pyroelectric properties. In addition, wurtzite has good biocompatibility and has been certified by FDA for the consequent use of ZnO in biosensors [91–93]. Many studies have reported that zinc oxide has antibacterial and stimulating effects on the growth of osteoblasts [94,95].

Fujimura *et al.* [96] deposited ZnO thin film on a $Si/SiO_2/Al$ substrate, and the transverse piezoelectric constant d_{31} of the ZnO thin film was −3.21 pC/N. Similarly, ZnO can be used as a coating on the commonly used orthopaedic implant Ti to provide piezoelectric, antibacterial and osteogenic properties. ZnO/TiO_2 nanoarray ($nZnO/TiO_2$) composite coatings were prepared by hydrothermal and low temperature liquid phase (LTLP) method. Under the periodic loading, a prominent increment of cytocompatibility and osteogenesis of MC3T3-E1 was attributed to the piezoelectricity of $nZnO/TiO_2$ [97]. Quan *et al.* [98] prepared ZnO coatings on titanium substrates by the same method and generated mechanical stimulation of ZnO by LIPUS to verify that the electrical stimulation generated by LIPUS-excited ZnO accelerated the proliferation and differentiation of osteoblasts. Zhao *et al.* [99] synthesized silver-ear-shaped ZnO by hydrothermal and microwave methods, and constructed ZnO-Col-I coating on titanium surface by adsorption of collagen type I (Col-I), which can resist bacteria such as Gram-positive bacteria, Gram-negative bacteria and Streptococcus mutants, and has a good photothermal conversion effect. With a photocontrolled warming effect under 808 nm NIR irradiation, the thermotherapy induced by this photothermal effect can promote the formation of new bone around the titanium implant, both antibacterial and osteogenic. Murillo *et al.* [100] cultured human osteosarcoma cells (SaOS-2) and macrophages on ZnO nanosheets, and ZnO generated an electrical signal in response to the intrinsic mechanical forces of the cells, stimulating the metabolism of SaOS-2 cells and macrophages. The electrical signal activated the opening of calcium channels on the cytoplasmic membrane, the inward flow of extracellular calcium ions and the increase in the amount of intracellular calcium ions, which all led to accelerated cell growth.

4.5. Boron nitride (BN)

There are four crystal forms of boron nitride (BN), which are isoelectronic with carbon lattice of similar structure: hexagonal boron nitride (h-BN), rhombic cubic boron nitride (r-BN), cubic boron nitride and wurtzite boron nitride (w-BN). Boron nitride ceramics are often used in the field of bone tissue repair in the form of low-dimensional nanomaterials, boron nitride nanotubes (BNNTs), to overcome the high brittleness and low strength of BN ceramics [101]. BNNTs has piezoelectric properties (not high in the radial direction but excellent in the longitudinal direction) and good biocompatibility and its piezoelectric property is better than that of common piezoelectric polymers [36,102]. Nitrogen is the adjacent element of carbon, so BNNTs and carbon nanotubes (CNTs) have similar structure and properties, but compared with CNTs, BNNTs has better oxidation resistance and chemical stability. BNNTs can also maintain stability in high temperature and strong acid and alkali environment and its redox temperature is as high as 900 °C, much higher than 400 °C of CNTs [103,104].

Li *et al.* [105] directly cultured mesenchymal stem cell mesenchymal stem cells (MSCs) in BNNTs, which proved the effect of BNNTs on osteogenic differentiation. The results showed that MSCs attached and grew well on BNNTs. BNNTs promoted the proliferation of MSCs and increased the secretion of total protein by MSCs. Especially, BNNTs enhance the alkaline phosphatase (ALP) activity as an early marker of osteoblasts, ALP/total protein and osteocalcin (OCN) as a late marker of osteogenic differentiation, which shows that BNNTs can enhance osteogenesis of MSCs. According to different preparation methods, the Young's modulus of boron nitride nanotubes (BNNTs) is generally in the range of 0.5–1.3 TPa [106], which is much higher than that of human bone, so BNNTs is not very suitable for the preparation of bone scaffolds alone.

4.6. Piezoelectric ceramic composites

Compared to polymer or ceramic materials, the stress/strain ratio of polymer/ceramic composites can be adjusted closer to bone [107], and despite higher biocompatibility, most of the piezoelectric ceramics are bioinert limiting their applications as bone filler for bioimplants. Therefore, piezoelectric ceramics are often combined with some polymers or polymer-ceramic composites as a piezoelectric component to form electroactive composites to obtain good cellular response and mechanical properties. These composites can overcome some disadvantages of piezoelectric ceramics themselves and have great potential for bone tissue engineering. Piezoelectric ceramic composites can be classified according to the nature of the material with which they are compounded into two categories: i) piezoelectric ceramics compounded with polymer materials and ii) piezoelectric ceramics compounded with ceramic materials. The type of material to be used for the composite is usually determined by the actual application and needs.

Composite of piezoelectric ceramics/polymers

Polymer materials often compounded with piezoelectric ceramics include some natural polymers with good bioactivity (such as chitosan, silk and so forth) or some synthetic polymers with good biodegradability (such as polycaprolactone, PCL), as well as polymers with their own piezoelectric properties (such as polyvinylidene fluoride, PVDF) which enhance the performance of piezoelectricity after compounding. The incorporation of polymeric materials in the composite enhances the biodegradability and mechanical properties of piezoelectric ceramic materials. The main purpose of using polymeric materials in the composite is to focus on the functionality of the material, with improvement in support being of secondary importance.

BT is a type of piezoelectric ceramics commonly compounded with polymers. Prokhorov *et al.* [108] reported the synthesis of a piezopolymer composed of chitosan (CS)/hydroxylated BT (OH-BTO) nanoparticles (NPs) with enhanced biocompatibility, non-toxicity and piezoelectric behaviour that could be advantageously used in biomedical applications. The nanocomposites exhibited a piezoelectric coefficient of d_{33} = 11.29 pC/N, demonstrating biocompatibility in contact with human fibroblast cells after 24 h. The cytotoxicity assays with human fibroblast cells revealed that the hydroxylation of BTO NPs did not affect the cell viability of CS/OH-BTO films with NP concentration from 1 to 30 wt.%.

PCL is often selected as a polymeric matrix material due to its thermoelastic behaviour, low melting point, ease of processing, remarkable mechanical strength and biocompatibility. Also, it is a food and drug administration-approved biodegradable polymer [109]. PCL/BT composite scaffolds were produced using a single-step extrusion-based 3D printing technology. The results showed that inclusion of 10 wt.% BT particles into the polymeric matrix improved the mechanical performance of the scaffolds. The bioactive surfaces of these scaffolds promoted the adhesion and proliferation of SaOS-2, with unique ALP activity and the deposition of osteocalcin and type I collagen [110]. Sikder *et al.* [111] introduced an innovative blend of electroactive and bioactive polymer-ceramics in the form of 3D-printable filaments. These filaments were specifically designed for use in fused filament fabrication 3D printing setups, enabling the production of design-specific piezoelectric orthopaedic scaffolds. The BT inclusion up to 25 vol.% enhanced the piezoelectric response gradually to 1.2 pC/N compared with the unmodified PCL specimen. However, the piezoelectric response increased significantly when the BT inclusion was above 25 wt.%. Specifically, the piezoelectric response increased to 2.4 and 2.6 pC/N for the PCL-BT (45 vol.%) and PCL-BT (65 vol.%) specimens, respectively. BT exhibits high d_{33} values (>191), but polymer-ceramic composites such as PCL-BT never exhibited such a high piezoelectric response because the BT particles were not densely packed in a polymer matrix. Moreover, such a high scaffold-mediated piezoelectric response was not needed for bone regeneration, as the bone itself exhibited a piezoelectric response in the range of 0.7–2.3 pC/N. Additionally, the mechanical properties of PCL-BT (25 vol.%) were the best among the three. However, the cell growth kinetics with PCL-65BT (65 vol.%) was the best due to the increased BT content, leading to enhanced proliferation and differentiation of preosteoblasts.

Polycaprolactone monoacrylate (PCLA) is another biodegradable material commonly used as a substrate material for piezoelectric ceramic fillers. BNNT can be compounded with degradable materials to construct biodegradable piezoelectric composites. In BNNT/PCLA composites, BNNT plays a positive role in mechanical properties and promotes osteogenesis. The composite containing 5 wt.% BNNT showed a remarkable increase of 1370% in elastic modulus. The gene expression study of osteoblast cells grown on the composite films showed four- and sevenfold increases in the expression level of the Runt-related transcription factor 2 (*Runx2*) in composites with 2 and 5 wt.% of BNNT, respectively [107]. All these positive results showed that the materials prepared from piezoelectric ceramics as electroactive fillers in polymers had great potential in bone regeneration. Such results were undoubtedly attractive. However, we need to pay attention to whether the precipitation of piezoelectric ceramics can cause harm to the human body during the degradation process.

Piezoelectric polymers have relatively good piezoelectricity, but their piezoelectric constants are much lower than those of common piezoelectric ceramics. Piezoelectric ceramics are often introduced into piezoelectric polymers to enhance the piezoelectricity of piezoelectric polymers while maintaining their good flexibility. BT particles, uniformly dispersed in the piezoelectric polymer PVDF as electroactive filler, induce the formation of β piezoelectric phase in PVDF. The β phase fraction of PVDF/BT scaffold was increased by 11%, resulting in an increase in output voltage by 356%. The enhanced electric cues could promote cell adhesion, proliferation, and differentiation more efficiently [112]. A smart piezoelectric nanohybrid was developed from poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) and BT [113]. Further, the electrospinning technique was adopted for the scaffolding to mimic the structure of natural cartilage. The scaffold with 20 wt.% BT showed enhanced mechanical properties and a piezoelectric coefficient (1.4 pC/N) similar to those of native tissue. It was a good promoter of tissue regeneration. The *in vitro* studies revealed improved cell adhesion and proliferation in poled scaffolds against unpoled scaffolds and PHBV due to improved d_{33}, thereby leading to larger surface potentials. Additionally, better gene expression revealed increased chondrogenic potential in poled nanohybrid scaffolds.

Similar to BT, other piezoelectric ceramics also can be compounded with piezoelectric polymers. Augustine *et al.* [114] prepared poly(vinylidene fluoride-trifluoroethylene) [P(VDF-TrFE)]/ZnO nanocomposite scaffolds with different ZnO contents. The results showed that the scaffolds had the best biocompatibility and ability to promote cell adhesion when the ZnO content was 2% (*w/w*). When the ZnO content exceeded 2% (*w/w*), the ZnO particles in the P(VDF-TrFE) copolymer matrix were poorly dispersed. The concentration of ZnO particles and their dispersion in the matrix affected, to some extent, their biocompatibility and ability to promote cell adhesion [115]. Some studies showed that zinc oxide possessed some cytotoxic properties and might reduce cellular activity [116,117]. Spindle-shaped submicron particles of ZnO were biocompatible. The inhibitory effect of ZnO films was related to their surface features and the inhibition rate was in the order of mesh ZnO film > lamellar ZnO film > granular ZnO film. In summary, the size of ZnO particles [118,119] and their morphology and surface characteristics are also factors that should not be ignored [119–123], besides the cytotoxicity caused by the concentration of ZnO. However, the cytotoxicity of ZnO can be overcome by some modifications [121,124]. The aforementioned findings indicated that the antibacterial and osteogenic activities of ZnO as a substitute for bone tissue engineering were fascinating. However, the cytotoxicity of ZnO should be properly resolved before clinical application.

Genchi *et al.* [125] prepared P(VDF-TrFE)/BNNT piezoelectric films. The P(VDF-TrFE)/BNNT piezoelectric films with 1 wt.% BNNT content showed better piezoelectric properties than the pure P(VDF-TrFE) (d_{31} increased by about 80%). When SaOS-2 cells were cultured on the surface of the composite film and exposed to LIPUS stimulation, the composite membrane produced piezoelectric signals. These signals, in turn, elicited a more robust cell response and promoted the differentiation of SaOS-2 cells.

The morphology and structure of the material have a great influence on its performance. Qian *et al.* [126] prepared BN nanosheets to surface-tailored PCL smart piezoelectric scaffolds using a combined approach of layer-by-layer droplet spraying technique. The scaffold was characterized by its hydrophobic, biocompatible and stiff behaviour. BT NPs are widely used for preparing organic-inorganic composites [127–129]. However, low concentrations of BT could not form interconnected electroactive networks in the polymer matrix and the composites were less electrically active. Liu *et al.* [130] showed that when the volume fraction of BT particles in PCL was less than 35%, the d_{33} of the composites ≤1 pC/N increased slowly when the content of BT was lower than 30 vol.%. The d_{33} of the composite with 40 vol.% BT increased to 3.9 pC/N, several times that of the composites with 35 vol.% BT [130]. BT nanofibres are promising alternatives for preparing composites because their one-dimensional morphology facilitates network formation through fibre overlap. Also, they can be embedded in the polymer matrix at a high-volume fraction without severe aggregation. The piezoelectric coefficient with 50 vol.% BT nanowires embedded in PVDF was 61 pC/N, which was much higher than that of nanocomposites with spheroid-shaped BT NPs as well as comparable to, if not better than, that of other NP-filled polymer composites [131,132]. Ca/Mn co-doped BT (CMBT) nanofibers were developed by Zheng *et al.* [133]. However, with the release of doping ions, CMBT nanofibres achieved significantly higher ability than BT nanofibres in inducing the osteogenic differentiation of bone mesenchymal stem cells (BMSCs). Although d_{33} of Ca^{2+}- and/or Mn^{4+}-doped BT nanofibers decreased with the increase in ion doping amount, it was approximately 0.9–3.7 pC/N and comparable to that of native bone (0.7–2.3 pC/N) at an optimized content. On this basis, Zheng *et al.* [134] prepared poly(l-lactide) (PLLA)/CMBT composite membranes by introducing different volume fractions of CMBT nanofibres into the PLLA matrix, as depicted in Fig. 11. The resulting PLLA/CMBT composite membranes exhibited higher d_{33} values in line with the content of CMBT nanofibres increasing from 0 to 20 vol.%, reaching 3.5 pC/N. The dispersion of the nanofibres in the polymeric matrix was poor and d_{33} value of the membranes levelled off when the amount of CMBT exceeded 30%, indicating the formation of the CMBT fibrous network within the PLLA matrix. BMSCs were cultured on PCL and PLLA/CMBT composite membranes (PCL was the control). Notably, the composite

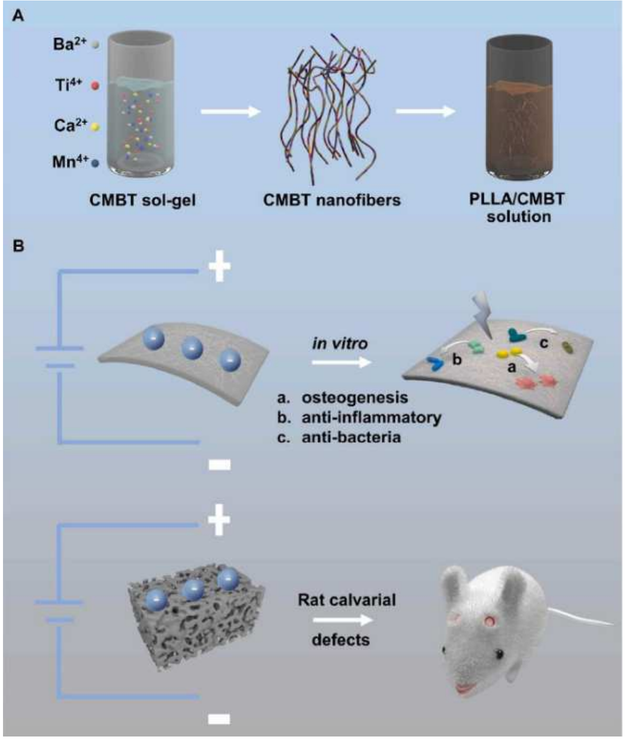

Figure 11. Preparation process, role and implantation experiment of PLLA/CMBT bone scaffold [134]

membranes exhibited a significant enhancement of cell proliferation and osteogenic differentiation. Similarly, porous scaffolds were fabricated for *in vivo* implantation in a rat bone defect model, where the piezoelectric PLLA/CMBT scaffold demonstrated substantial improvement in bone regeneration.

Composite of piezoelectric/bioactive ceramics

Piezoelectric ceramic components are usually introduced into ceramics-based materials to achieve piezoelectricity and enhance the mechanical properties of the composite to some extent. Common ceramics-based materials compounded with piezoelectric ceramics include hydroxyapatite and β-tricalcium phosphate. Hydroxyapatite is used as a suitable bone-filling and bone scaffold material because of its good bioactivity and biodegradability. Also, it exhibits a crystal structure similar to the inorganic phase of human bone [135]. In short, mineralized bone is 99% Ca^{2+} ions stored in the mineral form of HA. This native structural orientation justifies the importance of bioceramics, which are used in large quantities to make composite ceramic scaffolds for enhanced functional and structural support.

Dubey *et al.* [136] prepared a functionally graded material having a multi-layer composite structure, with KNN as the intermediate layer, HA as the upper and lower layers, and HA and KNN mixed in the ratio of 1 : 7 as the buffer layer between KNN and HA. The aim was to enhance the electrical activity of HA using KNN ceramics as the intermediate layer without affecting its biological activity. Through this strategy, the electric polarizability of HA was significantly improved and became similar to the electrical properties of bone (d_{33} = 4.2 pC/N). The value-added behaviour of human osteoblast-like SaOS-2 cells on the material was examined, revealing that KNN had a higher proliferation rate than other samples. The electroactivity of KNN might be the reason for its better cell proliferation compared with other samples.

BNNT often balances mechanical properties by compounding with other materials, while providing excellent piezoelectric properties for the composites. Lahiri *et al.* [137] explored BNNT as a reinforcing agent for HA in orthopaedic applications. HA-BNNT composites were synthesized using spark plasma sintering. HA-4 wt.% BNNT composites exhibited excellent mechanical properties, including a 120% increase in elastic modulus, 129% increase in hardness, 86% increase in fracture toughness and 75% increase in wear resistance compared with HA alone. The osteoblast proliferation and cell viability showed no adverse effects with the addition of BNNT. Therefore, HA-BNNT composites are envisioned as potential materials for stronger orthopaedic implants.

BT and HA are two most commonly used materials in piezoelectric ceramics and bone substitute materials, respectively. Hence, the composite of these two materials in bone tissue engineering needs investigation. Tang *et al.* [138] prepared HA/BT composites by slip casting and the piezoelectric properties were obtained by polarization. After polarization, HA/BT piezoelectric ceramics had d_{33} values between 1.3–6.8 pC/N, with $BaTiO_3$ content ranging from 80% to 100%. The best biocompatibility and bone-inducing activity were demonstrated by the 10% HA/90% $BaTiO_3$ piezoelectric ceramics [138]. The effect of adding BT to HA on the material properties was explored in depth by Tavangar *et al.* [139]. The HA-BT scaffold had higher compressive strength, toughness, density and hardness compared with the pure HA scaffold. More apatite deposited on HA-BT after the immersion of the scaffold in SBF solution, resulting in a rougher surface on this scaffold than pure HA. The piezoelectric properties of HA improved in the presence of BT. Composites containing 40, 50 and 60 wt.% BT had excellent biocompatibility. This study provided a basis for selecting the BT doping amount in the future.

In general, β-tricalcium phosphate (β-TCP) is preferred as a base bioceramics compared with other anisotropic forms of TCP due to its chemical stability, mechanical strength and moderate bioabsorption [140]. Additionally, among the various calcium phosphate compounds, β-TCP is the second most clinically used bioactive ceramic, exhibiting relatively higher solubility and inducing bone formation. Tariverdian *et al.* [8] prepared a barium strontium titanate (BST)/β-TCP composite electroactive scaffold by 3D printing using piezoelectric ceramic BST that could be spontaneously polarized, with β-TCP as the base bioactive material for the scaffold. None of the BST/β-TCP composites showed cytotoxicity when in contact with cells. Also, 60%

of the BST/40% of the β-TCP samples showed more mineral deposition. Osteosarcoma cells showed significantly higher ALP activity on the 60% BST/40% β-TCP samples than on the other composites. Modified BTs (barium zirconium titanate ceramics or $BaZr_xT_{1-x}O_3$) when doped with Zr exhibit better electrical properties compared with the unmodified BTs [141,142]. For example, $Ba(Zr_{0.07}Ti_{0.93})O_3$ showed a piezoelectric coefficient d_{33} > 290 pC/N with 2 wt.% B_2O_3 [143]. Barium zirconate titanate additive improved the electroactivity of the composites. *In vitro* bioactivity tests showed that the composites had higher apatite formation ability compared with BZT [144]. Therefore, the composites formed between BZT and calcium phosphate-based materials might yield better piezoelectric properties compared with the common HA/BT composites.

New bioactive ceramic materials with comprehensive properties, which may be superior to β-TCP and HA, have emerged in recent years. Calcium silicates such as akermanite ($Ca_2MgSi_2O_7$) with bioceramics containing Ca, Mg and Si have received more attention due to their controllable mechanical properties and degradation rates. Porous electroactive nanocomposites with suitable piezoelectric coefficients were fabricated by the freeze-casting technique from the barium titanate and nano-akermanite (BT/nAK) suspension [145]. The highest d_{33} of 4 pC/N was achieved for BT90/nAK10 (BT 90 vol.% and nAK 10 vol.%). The interconnected pore channels were observed in the scanning electron microscopy images. No detectable transformation phase was found in the x-ray diffraction pattern for the BT/nAK composites. The operational flexibility of this approach suggested the possibility of meeting customized needs in the application of bone substitutes.

Ceramics-based materials often require sintering or other post-treatment to enhance their mechanical properties, and scaffolds are often preformed. Although some structural designs can enhance mechanical properties, they cannot accommodate irregularly shaped bone defects. Wu *et al.* [146] developed an injectable and piezoelectric bone substitute based on calcium phosphate silicate (CPS) with piezoelectricity comparable to that of natural bone without any post-treatment. The *in vitro* analyses demonstrated that nano-$BaTiO_3$ (nBT)/CPS was biocompatible and could promote osteoblast differentiation. The ability to promote the proliferation and differentiation of osteoblasts was the strongest when the mass fraction of nBT in the composite was 40%, and the composite had the highest d_{33} value of 2.53 pC/N.

Other special types of compounds

In addition to these two categories of composite systems, there are also some more niche composite systems. Some are a composite system containing both ceramic materials, polymer materials and other materials (multi-material composite is the future trend). These composite systems are usually still in the preliminary exploration stage because of complex composite processes, high innovation or poor experimental reproducibility, so the number of research cases is not as high as the above two systems, but it does not mean that these composite systems are failures, and these studies outside the two main categories may be cutting-edge.

Carbon based conductive materials such as graphene and carbon nanotubes can be used to enhance the piezoelectricity of piezoelectric materials. Tang *et al.* [147] added BT particles to PMMA bone cement to make the composite material with piezoelectric effect. Based on this composite system, graphene was added and improved the piezoelectric coefficient by increasing the conductivity, dielectric constant and effective polarization voltage of the graphene (G)/BT/PMMA bio-piezoelectric composite, which could obtain a piezoelectric coefficient close to that of human bone at a relatively low BT addition (the addition of 2.5 vol.% of graphene to the BT/PMMA composite increased the piezoelectric constant value of the composite from 0.1 to 1.5 pC/N, the principle of which is shown in Fig. 12. This new composite material has potential applications in various fields such as oral cavity and bone immunity. Electrostatic spinning is a technology used to produce nanoscale fibres and was used to incorporate ZnO nanoparticles (ZnONP) in electrospun carbon nanofibres. The obtained composite possesses good flexibility and the presence of ZnONP improved structure formation with lower defect density. Cellular cytotoxicity assays revealed the good biocompatibility of ZnONP-

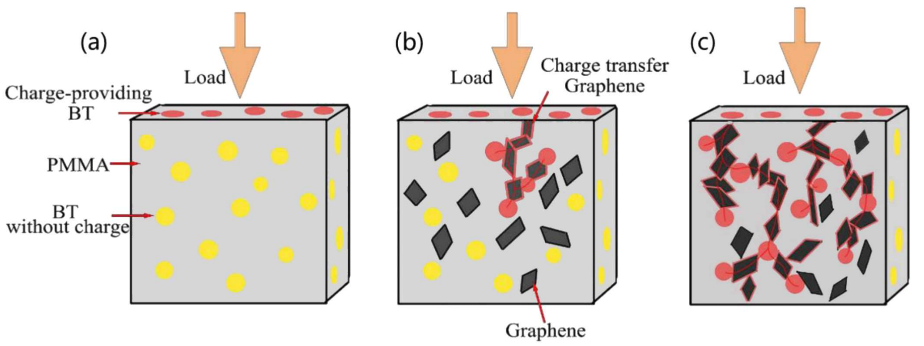

Figure 12. Improving mechanism of the piezoelectric coefficient of the G/BT/PMMA bio-piezoelectric composites by graphene addition: a) no graphene is added, b) a small amount of graphene is added and c) sufficient graphene is added [147]

carbon nanofibre (CNF) composites and MG-63 cells could attach and spread well on the nanocomposites with any concentration of ZnONP [148].

Ehterami *et al.* [149] prepared a BT/gelatin/nano-hydroxyapatite (nHA) composite bone scaffold using a special method. The scaffold was not actually compounded with materials. Rather, after the preparation of the BT piezoelectric scaffold was completed, the fabricated scaffolds were electrically polarized and coated with gelatin/nHA nonocomposite in order to improve their mechanical and biological properties. The material had good biological activity and piezoelectric properties, which provides a new idea for using the diversified functions of electroactive composite materials to repair bone tissue. However, there are requirements for the biocompatibility and mechanical properties of materials used in bone tissue engineering. Considering that the original functions of the composite materials will change, the composite of ceramic materials and polymer materials or metal materials is not as simple as imagined, related theories still need to be further studied and verified by experiments.

V. Challenges and prospects

Healthy bone tissue produces endogenous electrical signals that affect regeneration by activating ion channels on the plasma membrane. The production of endogenous electrical signals is impaired when bone is damaged. The repair and regeneration of bone tissue are promoted by compensating for the interrupted endogenous electrical signal in the damaged bone tissue; that is, transmitting the electrical stimulation to the site of the bone damage. All kinds of piezoelectric ceramics present good osteogenic activity, which shows that they are suitable as materials to promote bone tissue repair and regeneration. However, at present, only a few materials have entered the stage of *in vivo* research as bone implant materials, and most of the materials are still being studied *in vitro*, and some of them are even controversial about biocompatibility. The key problem of whether these piezoelectric ceramics can be used in bone tissue engineering is whether these materials can be verified by cytotoxicity experiments. Most piezoelectric ceramics have the phenomenon of ion dissolution in body fluids. However, among the dissolved ions, except Pb^{2+} that has been proved to be toxic, other ions may be cytotoxic at high concentrations, but at low doses they are relatively safe and even beneficial. Therefore, in the subsequent studies of piezoelectric ceramic implantation, more attention should be paid to controlling the dissolution of ions. Since the toxicity of the released ions depends on their concentration, the incorporation of piezoceramics embedded into a polymeric matrix would help control ion dissolution. However, when working with biodegradable polymer-based formulations, the degradation products of the nanocomposite have to be removed from the body via human metabolism to avoid long-term risks, and also uncontrollable agglomeration of piezoelectric ceramic nanoparticles needs to be monitored. In the future, a large number of cytotoxicity experiments are needed to further clarify the biocompatibility issue. And *in vivo* experiments should be accelerated, as *in vitro* experiments alone cannot achieve convincing progress.

Different tissues have different responses to electrical stimulation, different tissues have suitable electrical signal range values for their growth, and even different sizes of electrical stimulation may lead to different differentiation results. At present, we only know that electrical stimulation can promote the repair of bone tissue, and the effective range of electrical stimulation on bone cells and bone tissue cannot be determined. Accurately controlling the value of electrical stimulation is also a challenge that we will face in the future. For piezoelectric ceramics, it is necessary to consider how to control the intensity of the piezoelectric signal obtained by stimulating the piezoelectric effect *in vivo*, and whether the piezoelectric signal can be controlled by non-contact mechanical stimulation such as ultrasound for large bone defects.

Piezoelectric ceramics can induce bone tissue regeneration by generating electrical signals in response to mechanical stimuli, but a single ceramic material cannot meet the requirements of bone tissue repair and cannot avoid the shortcomings of the material itself, so a multi-component material composite is required to achieve the effect of bone tissue repair. In addition to electrical properties, the most basic properties of multi-component materials should include good biocompatibility and suitable mechanical properties. Moreover, antibacterial properties are also one of the important properties of bone repair materials. In the future, it can be developed towards the direction of piezoelectric conductive composites, both electrical signal generation and transmission, complementing each other's strengths, and achieving suitable mechanical properties and biocompatibility by compounding with other materials, on the basis of which the electroactive biomaterials are combined with various types of proteins, growth factors, etc. adding molecules such as antibacterial components, drug slow release systems, etc. to fully enhance processes that the electroactive biomaterials can stimulate. The potential of electrophysiological microenvironment in living biological tissues can be fully utilized to achieve multi-functional integration for the purpose of promoting bone repair.

VI. Summary

This review briefly describes the background of the development of electrically stimulated osteogenesis and the association of electrical stimulation with bone tissue repair, and illustrates the importance of constructing an electrical microenvironment for bone tissue recovery and regeneration. The way in which piezoelectric materials produce piezoelectric effects and the basic principles of piezoelectric effects are described, and the effects of piezoelectricity on cells and animals *in vivo* and *in vitro* are emphasized. Representative materials such as BT, LKNN, and ZnO in the field of bone tissue engineering, the current state of development, and the principles of their applications are analysed in depth. The main application modalities and current development bottlenecks of each piezoelectric ceramics are summarized. Although the development of piezoelectric ceramics is facing many challenges, it is still developing rapidly. In the future, through the compounding of materials, functional integration and complementary properties, piezoelectric ceramics are likely to become an intelligent repair material in the field of bone tissue engineering.

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