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Review Article

Next Generation Bone Biomaterials: Integrating Magnesium Phosphate and Piezoelectricity for Enhanced Osteogenesis

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The regeneration of bone tissue is one of the most important challenges in the orthopaedic reconstructive surgery because of the limitations of the traditional bone grafts. Recent progress in bone heal over the last decade has highlighted the importance of bioactive and biodegradable biomaterials that have the capacity to actively induce osteogenesis due to their ability to replicate physicochemical and electrical characteristics of natural bone. In this context, biomaterials based on Magnesium phosphate (MgP) have received a considerable attention due to their excellent biocompatibility, fast setting capacity, controllable degradation, and osteogenic capability. Besides chemical stimulation, electrical stimulation is also important in natural bone remodelling because bone tissue is intrinsically piezoelectric. Therefore, Piezoelectric biomaterials become a promising approach to replicate the intrinsic electromechanical behaviour of bone. These substances produce electrical responses in response to mechanical stimulation to encourage osteoblast adhesion, growth, angiogenesis, and mineralization. The inclusion of these piezoelectric elements in magnesium phosphate matrices would offer a versatile platform to deliver synergistic ionic, structural as well as electrical signals to promote bone healing. Recent developments have centred on using piezoelectric materials with magnesium phosphate scaffolds in order to create multifunctional composite scaffolds which can synergistically impart ionic, structural, and electrical stimulation to stimulate bone regeneration. This review comprehensively discusses the different types of magnesium phosphate biomaterials and piezoelectric materials, their physicochemical properties, mechanisms underlying osteogenic stimulation, recent composite strategies, and current challenges toward clinical translation. The integration of MgP-based systems with piezoelectric materials considered as promising direction for next-generation smart scaffolds in bone tissue engineering.

Introduction

Bone defects and injuries that result due to trauma, degenerative diseases, birth defects, and tumor excision are a deadly clinical issue. Even though the autografts which have remained the standard of bone repair levels have their own flaws such as donor site morbidity, low availability as well as complications, the autografts have necessitated the creation of synthetic bone replacements that are more biological and mechanical in nature [1]. The concept of smart bone substitutes has been recently introduced, and the main focus is put on biomaterials that do not merely provide structural support when introduced into the body but also involve in bone healing process by being bioactive, biodegradable, and responsive to physiological stimuli.

Magnesium phosphate cements (MPCs) are one of the advanced materials which have been receiving a lot of interest as new generation bone substitutes. The MPCs possess a low setting time, high initial mechanical strength and a degradation rate that can be tuned as opposed to the traditional calcium phosphate cements therefore they can be utilized in a wide variety of clinical uses such as fracture fixation, bone defects repairing, and more. It is worth noticing that magnesium ions play a fundamental role in the metabolism of bones and can stimulate the activity of osteoblastics and the development of new bones thereby enhancing the regenerative skeleton of these substances [1,2]. According to recent studies, magnesium phosphate is a third-generation bioresorbable ceramic with tunable property, enhanced osteogenesis and can be fabricated using advanced technologies including 3D printing to produce patient specific implants [3].

Simultaneously with these advances, piezoelectric biomaterials have

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shown up as a novel type of material that replicates the natural electromechanical behaviour of bone. Piezoelectricity is intrinsic to bone tissue and the material emits electrical responses to mechanical forces that control cellular activities, including cell growth, cell maturation, and cell mineralization [4]. By integrating piezoelectric materials such as barium titanate or piezoelectric polymers in bone scaffolds, the bioactive systems such as electrical stimulation of the bone regeneration without external sources of power can be developed. More recent developments have shown that piezoelectric components with calcium or magnesium phosphate cements can support osteogenic reactions and in load bearing implantation to a high extent and create multifunctional bone substitution [5].

The integration between magnesium phosphate cements and piezoelectric biomaterials is a good strategy of producing multifunctional bone substitutes that are very close to structural, chemical, and functional properties of natural bone. The advantages of this type of hybrid systems are synergetic, which are mechanical stability, controlled biodegradation, osteoinductivity, and electromechanical stimulation. This review seeks to get a general picture of the recent advances in magnesium phosphate cements and piezoelectric biomaterials on their respective features, with regard to the future development of smart bone substitutes to be effective in bone tissue regeneration.

Bone Biology and Osteogenic Repair

Structure and remodelling of bone tissue

Bone is a delicate element of the skeleton, function as a load-bearing structural material while simultaneously serving metabolic hematopoietic and regenerative roles. The trabecular and cortical bone (figure 1) are the two distinct elements which make up the bone and play a typical role [6]. Numerous organic and inorganic contribute to the multifaceted nature of bone. At molecular level, bone consist of organic phase such as Type I collagen which provide tensile strength and toughness and mineral phase comprising poorly crystalline, carbonated hydroxyapatite [7]. A complex hierarchical structure of bone is scrutinized as solid hydroxyapatite crystal and congealed by collagen fibres. Release of collagen fibres by the osteoblast and extracellular ground matrix result in the make-up of osteoid which strengthen the flexibility and structure of the bone [8].

Bone remodelling a physiological process that is highly monitored and perpetually preserves skeletal integrity by harmonizing bone resorption and bone creation (figure 1) [9]. This process takes place by the synchronized action of mediated bone resorption followed by osteoblast driven bone formation, which takes place in the distinct anatomical structure known as Basic Multicellular Units (BMUs). Recent research highlights that remodelling is a highly complex process were resorption and formation are physiologically and chronologically interrelated to ensure the substitute of old or micro damaged bone with freshly mineralized tissue [10].

Osteoblast and osteoclast interaction is controlled by extensive bidirectional signalling pathways at the cellular and molecular levels. During bone disintegration, osteoclast release coupling factors like transforming growth factor-β (TGF-β), insulin-like growth factors (IGFs), sphingosine-1-phosphate, and cardiotrophin-1. Osteoblast-lineage cells and osteocyte predominantly influence osteoclast differentiation via the RANK–RANKL–OPG signalling axis. These factors directly relate bone resorption to subsequent bone formation by activating osteoprogenitor cells and encourage osteoblast differentiation [11]. The concept of tight functional linkage rather than independent cellular activity is reinforced by recent reviews that demonstrate osteoclasts are active regulators of osteogenesis rather than resorptive cells.

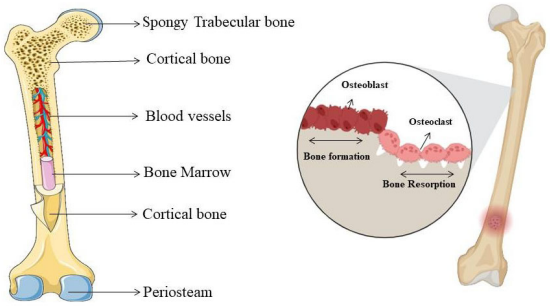

Figure 1: Structure of bone and bone remodelling

Role of mechanical and electrical cues in bone healing

Mechanical loading and endogenous electrical signals, which are physical cues, contribute an important role in the coordination of the cellular response and tissue restoration and are the ones that sustain the osteogenic pathway. Daily activities cause the formation of physical forces that are then transduced into biochemical signals within the body influencing the process of mechanotransduction, which regulates cell division, growth and differentiation [12]. Mechanosensitive proteins and ion channels, such as Pizeo1 have been found to show active response towards mechanical loading, which facilitate early stage bone repair by promoting osteoblast activity and matrix deposition near implants and fracture sites. Such directional loading not only changes cellular behaviour but also influence tissue architecture and boost local bone formation, Implying that mechanical signal serve as essential promotors of bone regeneration [13].

Apart from mechanical stimulation, bioelectrical signals secreted by bone tissue or administered externally have significant effect on bone regeneration. Electrical signalling has been observed to enhance the mesenchymal stem cell differentiation into osteoblasts, speed mineralization, and refine osteogenic signalling pathways such as BMP and Wnt/β–catenin, which improve fracture healing and bone formation. Other externally applied electrical stimulation methods including direct current, pulse electromagnetic fields and scaffold-based piezoelectric stimulation were also discovered to stimulate angiogenesis and osteogenesis in preclinical studies highlighting the therapeutic promise of electrical cues in regenerative medicine [14].

The interaction of mechanical and electrical stimuli is believed to be the vital part in bone healing. Mechanically generated piezoelectric can mimic the conventional electric environment of bone, thus enhancing cellular mechanotransduction and downstream anabolic pathways. The new scaffold designs take advantage of this synergy and use piezoelectric substances that transfer electrical impulses with mechanical loading, which causes self-powered electrical stimulation that enhances osteoblast proliferation, extracellular matrix development and association with host tissue. These new generation biomaterials have a higher regenerative ability because they replicate the natural biomechanical and bioelectric addicts of bone, confirming the idea of combination of mechanical and electrical impulse is best to repair and restore bone functions [15,16].

Magnesium-based biomaterials for bone repair

Biological role of magnesium in bone metabolism

The second mineral cation, which is the most abundant, is magnesium, which has a far-reaching impact beyond mere structural support. Physiological levels of magnesium at the cellular level influence the behavior of osteogenic progenitor cells, pushing them towards proliferation and differentiation via Wnt/ β-catenin, PI3K/Akt, and p38/MAPK. These signals eventually converge on transcription factors like Runx2 and Osterix, and are central to osteoblast maturation and matrix mineralization. Meanwhile, magnesium seems to maintain osteoclastic activity by modulating the RANKL to OPG ratio in a subtle manner and attenuating NF-kB-mediated osteoclastogenesis [17,18].

Magnesium phosphate cements and ceramics

The magnesium phosphate cements in the context of bone repair, have fast-setting and they form functional mechanical strength at an early stage which is reassuring in a situation where a defect needs to be supported immediately after the implantation. Simultaneously, they are also biodegradable when compared with most of the traditional cemeteries,

releasing magnesium ions in the process. These ions do not just pass by; they are capable of affecting local biological signalling, and pushing the cells towards osteogenesis and even angiogenesis inside the defect. Researchers have strived to refine compositions and surface features to create a balance between strength and bioactivity, and is a move in the direction of designs that are not completely controlled by laboratory methods, to designs that can be potentially useful in a surgical context [19].

A wider range of forms of magnesium phosphate ceramics have been studied, especially in terms of porosity, crystal chemistry, and ion substitution. Variations in pore size and trace ion incorporation influence the dissolution rate of the ceramics and the activity of osteoblasts. One of the arguments used to justify the continued use of MgP ceramics is that they will degrade more naturally at a rate more compatible with the rate of bone formation, and no longer be retained where they are not necessary [20].

In recent times, composite strategies have started to erase the lines between ceramics and the softer biomaterials. Incorporation of magnesium phosphate phases and polymers or secondary inorganic materials is likely to solve several practical challenges faced in the field like injectability and handling among other benefits in enhancing biological performance. Magnesium tends to promote VEGF expression and supporting endothelial cell migration, it helps couple osteogenesis with angiogenesis, ensuring that newly forming bone is supplied with oxygen, nutrients, and circulating progenitor cells [21].

Physical property & osteoconductivity

Physicochemical characteristics of magnesium-based biomaterials tend to prevail, which makes their behaviour different compared to the more common calcium phosphate systems. Specifically, magnesium phosphates become highly surface reactive and exchange ionic with physiological media. Their crystal chemistry allows gradual dissolution of magnesium ions as the substance reacts with body fluids and therefore regulates local pH and ionic composition. Although this reactivity may be beneficial, allowing biological signalling that may support osteogenesis, it also provides some degree of uncertainty. Even small differences in composition, particle size or crystallinity may significantly affect solubility and surface behaviour, which makes standardisation across studies more challenging [22].

The release of magnesium ions can locally increase the pH, although the calcium and phosphate ions which surround it can reprecipitate to create a more bone-like apatite layer- the process which is linked to better bone bonding. Osteoconductivity is one of the main characteristics that are continuously reappearing that is assisted by the biomaterials in repairing bone. This is in simple terms the capacity of a material that can be used as a scaffold on which bone cells can bind to, grow on and ultimately be substituted by the native tissue. Materials that are osteoconductive invite new bone growth by supporting cell adhesion and differentiation. In the context of magnesium-based biomaterials, the release of magnesium ions plays a dual role: the physical structure

Table 1: Magnesium Based Biomaterials used in Bone Repair

Material type	Composition	Degradation behaviour	Osteogenic effect	Limitation
Pure magnesium (Mg) [25,38]	Mg (≥99.9%)	Rapid corrosion in physiological fluids; releases Mg^{2+} and OH^-	Promotes osteoblast adhesion and bone mineralization	Excessive degradation, hydrogen gas evolution, local alkalization
Magnesium alloys [39,40]	Mg–Ca, Mg–Zn, Mg–Sr, Mg–REE	Controlled degradation compared to pure Mg; tunable corrosion rate	Enhanced osteogenesis, angiogenesis, and mechanical support	Alloying elements may cause cytotoxicity; corrosion heterogeneity
Magnesium oxide (MgO) [26]	MgO nanoparticles or coatings	Slow dissolution; pH buffering effect	Improves osteoblast proliferation and antibacterial activity	Brittle; limited load-bearing capability
Magnesium phosphate cements (MPCs) [41]	MgO + phosphate salts (e.g., KH_2PO_4)	Self-setting; resorbable with ion release	Enhances bone regeneration and defect filling	Short setting time; heat generation during setting
Mg-based composite scaffolds [42,43]	Mg/MgP + polymers (PLGA, collagen, gelatin)	Polymer phase moderates Mg degradation	Improved cell adhesion, osteogenic differentiation	Complex fabrication; batch variability
Surface-modified Mg biomaterials [44]	Mg with Ca-P, polymer, or ceramic coatings	Reduced corrosion rate and improved stability	Enhances osseointegration and early bone healing	Coating delamination risk
Mg-Ca based alloys with CaP coatings [45]	Mg-Ca + Zn/Ga-doped CaP coatings	Reduced corrosion and tailored degradation	Enhanced bone formation in large defects	Complexity of coating process
Mg-MOF composite hydrogels [46]	Mg-metal-organic frameworks (Mg-MOFs) + gelatin	Slow Mg^{2+} release; sustained ion delivery	Promotes M2 macrophage polarization & osteogenesis	Potential immunogenicity; complex synthesis
Mg phosphate cements/ceramics [18]	$Mg_3(PO_4)_2$, TMP, Mg–P based cements	Self-setting; moderate resorption	Good osteoconductivity, supports apatite formation	Brittle; limited mechanical strength
Mg-doped bioceramics & composites [18]	Mg-doped bioglass, Mg_2SiO_4, $Ca_2MgSi_2O_7$ composites	Controlled dissolution; releases Mg^{2+} & Si^{4+}	Enhances osteointegration & promotes bone repair	Processing challenges
3D-printed porous Mg scaffolds [47]	Additively manufactured Mg alloys	Porosity controls degradation	Biomimetic structure; enhanced vascularization	Additive manufacturing complexity
Surface-modified Mg implants [48]	Mg with PEO, Ca-P, polymer coatings	Reduced corrosion; tailored interface	Improved osseointegration and stability	Possible coating delamination

of the scaffold helps guide bone ingrowth, and the local chemical environment created by Mg^{2+} further encourages cells to behave in a way that builds bone. Magnesium ions have been shown to interact with cellular signalling pathways that influence osteoblast activity, including pathways like Wnt/β−catenin and BMP/SMAD, which are well known for their roles in driving osteogenesis [23,24].

Role of magnesium phosphate in osseous repair

Magnesium phosphate (MgP) biomaterials being a natural component of the bone tissue are considered as an essential part of the skeletal metabolism and therefore, have become a promising candidate due to their high level of biodegradability and improved biological performance. MgP has a high resorption rate unlike the more traditional hydroxyapatite based materials that instead of the material remaining at the defect site the MgP is removed faster and is more representative of the physiological remodelling process of bone [25,26]. The controlled release of Mg^{2+} ions on degradation is one of the central mechanisms of the osteogenic potential of MgP. It is well known that the presence of magnesium ions enhances osteoblast adhesion, proliferation and differentiation through the stimulation of Wnt/β−catenin, MAPK and integrin-mediated adhesion signalling cascades [27-29]. In addition, Mg^{2+} ions increase alkaline phosphatase (ALP) activity and mineralization of the extracellular matrix and, hence, accelerate the formation of new bone [30].

Magnesium phosphate cements have received a lot of appeal in clinical and pre-clinical research studies, owing to their quick settings, injectability as well as their strong early mechanical strength. These self-setting matrices have the ability to adapt to the discontinuity of the bone defects and harden in place, thus providing instant structural support [31,32]. Compared to calcium phosphate cements, MPCs have better compressive strength and better degradation kinetics. Moreover, their porous microstructure promotes cellular infiltration, vascularisation and bone ingrowth that further increase regenerative outcomes [33,34].

Recent advances focus on modifying MgP systems through ion doping (e.g., Zn^{2+} , Sr^{2+} , Si^{4+}) or composite fabrication with polymers and bioactive nanoparticles to further improve biological and mechanical properties [35,36]. With such modifications, degradation behaviour can be customised, osteoinductivity increased, and excessive alkalinity reduced in the initial stages of degradation. Moreover, incorporation of magnesium phosphate matrices with growth factors or piezoelectric materials has presented new possibilities of multifunctional scaffolds to provide chemical, structural as well as electrical signals in support of bone healing [37].

Piezoelectric biomaterials in bone tissue engineering

Fundamentals of piezoelectricity in biomaterials

Piezoelectricity refers to the capacity of some materials to produce electrical charge when they are under mechanical tension and vice versa. It is an electromechanical coupling, as the crystal structure of the material does not contain a centre of symmetry. The hierarchical structure of collagen fibres in the bone is twisted, and when the bone is bent or loaded, the bones will generate tiny electrical charges which are thought to participate in the way bone cells sense and react to mechanical forces. The concept of a material which is able to convert mechanical motion to electrical signals without an external power source, has floated the interest of researchers in smart scaffolds of bone repair [14,56].

It has been suggested that the endogenous piezoelectric effect of natural bone, which is largely due to its organic matrix, can be used to translate mechanical signals into bioelectric signals to regulate cellular behaviour, such as differentiation and matrix synthesis. This observation has prompted a series of research where engineers have actively engineered synthetic piezoelectric biomaterials towards the replication of these inherent electrical stimuli. The scaffold materials (like barium titanate piezoelectric ceramics or PVDF polymers) can create local electric fields due to mechanical deformation that is of interest, and may stimulate osteogenic reactions in the absence of batteries or external stimulation [56,57].

Natural piezoelectricity of bone and its significance

Bone is not just a structural material and a passive material; it has an insidious endogenous electrical life, which is especially salient when physi-

Table 2: Different types of Magnesium phosphate cements & Ceramics

Type	Chemical Formula	Setting Mechanism	Compressive Strength	Biomedical Application
K-struvite magnesium phosphate cement [49]	$KMgPO_4·6H_2O$ / K-struvite	Acid–base hydration $MgO + KH_2PO_4 \rightarrow$ struvite	~20–40 MPa	Bone defect filler; injectable bone cement
Chondroitin sulfate-functionalized MPC (CMPC) [50]	$KMgPO_4·6H_2O$ + CS coating	Surface lyophilization improves hydration	Improved vs. unmodified MPC	Promotes osteogenesis & angiogenesis
All-in-one injectable MPC [51]	MgO + phosphate salts	Self-setting; mild exothermic reaction	High early strength	Bone repair, fracture adhesion, osteoporotic fixati
Zn-doped calcium–magnesium phosphate cement [46]	Struvite + Zn dopants	Struvite formation with Zn inclusion	~20–25 MPa	Bone repair with antibacteria properties
TMP-based ternary cement (TMPC) [48]	$Mg_3(PO_4)_2$ + KDP + H_2O	Acid–base hydration yielding TMP/KDP phases	Moderate – high	Bone void filler, controlled degradation
MPC + Calcium silicate composite cement [52]	MgO/KH_2PO_4 + Ca-silicate.	Dual hydration reactions	Enhanced sustaining strength	Structural support & bone repair
Bioactive gelatin-methacrylate incorporated MPC [30]	MPC + GelMA	Polymer network enhances setting	Comparable to MPC, improved bioactivity	Bioactive scaffold/cement
Newberyite cement [53]	$MgHPO_4·3H_2O$	Acid–base hydration forming newberyite	~9–14 MPa (varies w/ formulation)	Resorbable bone substitute
Struvite/Magnesium oxychloride cement [54]	$MgNH_4PO_4·6H_2O$; $Mg_3(OH)_5Cl·4H_2O$	Mixed phase setting	Variable (~low-mod)	Bone filler; experimental compositions
Amorphous magnesium phosphate cement [55]	$Mg_3(PO_4)_2$ (amorphous)	Hydration → amorphous set	Variable depending on binder	Investigational bone cement

ologically loaded. These facts result in minute electrical charges being produced within the matrix of bone when the bone is bent or compressed, as part of normal activity, in walking or lifting, etc. a resultant of the intrinsic anisotropy of collagen fibres. The asymmetric fibres undergo deformation which causes internal charge distributions to be shifted and results in the formation of surface charges. This endogenous piezoelectric effect seems to be in good agreement with how bone tissue perceives and responds to mechanical signals. These charges regulate the transport of ions and cellular signalling and hence, affect the behaviour of bone cells in the process of remodelling and repair [15,58].

These piezoelectricity of the collagen fibrils at each micro-movement, step, jump or stretch, generates local electric fields, which can direct osteogenic cells to be where there is a load and at the same time coordinate remodelling. Basically the skeleton is an intrinsic electrophysiological feedback mechanism: mechanical stimulators cause electrical impulses which in turn feed back into cellular pathways that control bone formation and resorption. Recent research even suggests that natural collagen scaffolds maintaining this natural piezoelectricity are able to enable bone growth and angiogenesis under mechanical stimulation [59].

However, the importance of piezoelectricity of bone should be considered with a degree of sensitivity. It is not the only electrical or mechanical signal to influence bone biology and the comparative role of piezoelectric charge in bone biology compared to other signalling pathways of fluid flow and mechanotransduction is still being actively studied. Mineral constituents such as hydroxyapatite can play a role by associated electromechanical processes, including flexoelectricity, and confound the differences between discrete bioelectric processes. However, this inherent electrical behaviour provides a strong biological basis in the development of biomaterials that simulate or enhance the native responses of the bone especially where the objective is to produce implants that not only elicit a response to mechanical loading but necessary to engage in the healing process which is the coupling of mechanical loading and cellular responses[59,60].

Types of piezoelectric biomaterials used for bone repair

Besides the ceramics materials, piezoelectric polymers have also been the subject of interest in the bone and other tissue engineering circles due to their ease of creation as flexible and porous scaffoldings that better mimic the biomechanical environment of bone and at the same time, produce local electrical signals as a result of deformation. Biomaterials used in piezoelectric bone repair are divided into a few different families all with their unique advantages and disadvantages.

Role of piezoelectric materials in bone tissue repair

The piezoelectric materials used in bone tissue engineering applications have shown promising osteogenic potential with barium titanate ($BaTiO_3$), zinc oxide (ZnO), potassium sodium niobate (KNN), and boron nitride nanotubes (BNNTs) piezoelectric materials [82]. These materials form surface charges which support protein adsorption, cell adhesion and osteoblast proliferation, under dynamic loading. The electrical signals then trigger the voltage-gated calcium channels and other related intracellular signalling pathways, which ultimately lead to the up-regulation of osteogenic markers including alkaline phosphatase (ALP), osteocalcin (OCN) and Runx2 expression [83,84].

Flexible, biocompatible, and tunable piezoelectric coefficients have also made polymeric piezoelectric materials, especially polyvinylidene fluoride (PVDF) and copolymers (e.g., PVDF -TrFE) extremely attractive. Recent efforts focus on the integration of piezoelectric ceramics and polymers with composite scaffolds with bioactive matrices of cal-

Table 3: Piezoelectric biomaterial for bone regeneration

Material	Type	Piezoelectric Coefficient	Advantage	Limitation
PVDF (Polyvinylidene fluoride) [61]	Synthetic piezoelectric polymer	~20 pC/N	High flexibility; good piezoelectric output; supports cell adhesion	Non-biodegradable; may lead to fibrotic encapsulation
PVDF-TrFE (Copolymer) [62]	Synthetic piezoelectric polymer	~30 pC/N	Higher piezoelectric response than PVDF; supports multiple tissue regeneration	Still non-degradable; processing may be complex
PVDF-based composites (PVDF-ZnO, coatings) [63,64]	Polymer/ceramic composite	~6.5 pC/N or 3–4× PVDF	Enhanced output; improved osteoconductivity	Fabrication complexity; stability issues
$BaTiO_3$[65,66]	Lead-free ceramic	~191 pC/N	Very high output; biocompatible; osteogenic	Brittle; non-degradab
$BaTiO_3$ composites (polymer, collagen, HA) [67-70]	Ceramic composites	~1.3–6.8 pC/N (variable)	Tunable; promotes osteogenesis & angiogenesis	Dispersion & processing challenge
PHB & PHBV[68] [71]	Biodegradable polymers	~1.3–3 pC/N	Biodegradable; bioactive	Lower output than PVDF
PHB-$BaTiO_3$ composites [68]	Biodegradable composite	Enhanced vs PHB	Improved bone regeneration; ultrasound responsive	Needs in vivo optimization
PLLA [62]	Biodegradable polymer	d_{14} ~ −10 pC/N	Biocompatible; biodegradable	Requires shear mode lower efficiency
Natural polymers (Collagen, Chitosan, Cellulose, Silk) [72-75]	Natural biomaterials	~0.2–18.4 pC/N	Biomimetic; biodegradable; supports cell growth	Weak output; mechanical limits
ZnO [76]	Piezoelectric ceramic	Moderate	Osteogenic; biocompatible (bulk)	Nanotoxicity risk
Advanced piezo nanomaterials (BNNT, KNN, $CaTiO_3$) [76-79]	Emerging materials	Variable	High strength; lead-free; promising	Limited biological validation
Piezoelectric hydrogels & peptide-based materials [80,81]	Smart biomaterials	Variable	Mimic tissue mechanics; highly biocompatible	Early-stage research; low output

cium or magnesium phosphates, and therefore attain synergistic effects [85-87].

Synergic effects of magnesium phosphate and piezoelectric material

The natural bone has an inherent piezoelectricity and releases ions like Mg^{2+} and $(PO_4)^{3-}$ during remodelling, which are essential osteogenesis, angiogenesis and cellular signalling drivers [88]. Magnesium phosphate itself is also widely studied due to its osteoconductive and degradable characteristics and more recent studies have examined doped MgP and incorporating composite formulations specific to individual regenerative functions. It is the combination of piezoelectric materials and magnesium phosphate (MgP) that has become promising strategy to develop multifunctional scaffolds; to synergize bioactive ion release and electromechanical stimulation to support bone tissue regeneration [89].

Recent advances in injectable piezoelectric composite bone cements incorporating magnesium phosphate highlight the translational potential of these multifunctional materials for minimally invasive orthopedic applications. Researchers have developed injectable calcium–magnesium phosphate cements doped with piezoelectric particles such as zirconium-stabilized barium titanate (BCZT), achieving desirable setting behavior and mechanical strength while imparting piezoelectric properties that mimic bone's native electric response under mechanical stress. These piezoelectric features are expected to enhance local electrochemical signalling and osteogenic differentiation at defect sites, accelerating the healing process [90].

Despite these promising results, there are still a number of issues to be solved in order to optimise the balance between rate of degradation, electrical output, and biological performance of MgP/piezoelectric composites. The design of the scaffolds should be in such a way that they should provide sufficient piezoelectric response during physiological loading without undermining the integrity of the scaffold or causing accelerated degradation. Recent literature has highlighted the need to modify the porosity, phase composition, and fabrication techniques to achieve such a balance and the need to regulate the kinetics of magnesium ions release to avoid cytotoxic concentrations and, nevertheless, facilitate effective osteogenesis and angiogenesis [88]. Future research in these multifunctional composites has a great potential in providing the next-generation bone tissue engineering devices that can utilize biochemical and biophysical signals to achieve higher regeneration.

Degradation-electrical performance relationship in magnesium phosphate-piezoelectric composites

One important problem in magnesium phosphate–piezoelectric composite scaffolds is that these scaffolds lose their electromechanical efficiency during the degradation process. The piezoelectric effect is related to the effective transfer of the external mechanical strain applied to the surrounding magnesium phosphate matrix to the embedded piezoelectric phase. Thus, there is a paradox in the biodegradation of the magnesium phosphate matrix: biodegradation is desired in order to be replaced by newly formed bone; however, an excessive loss of the structural mass may decrease the efficiency of the mechanical load transfer necessary for continuous electrical stimulation [91].

The entire magnesium phosphate matrix is mechanically stiff enough to distribute physiological loading evenly to the embedded piezoelectric particles or fibres during the early stages after implantation. In such cases, the daily physical loading can be efficiently translated to local electrical signal, which can promote osteogenic differentiation. As degradation proceeds, however, the dissolution of magnesium phosphate phase increases the porosity of the scaffold, decreases the strength and weakens the matrix continuity of the scaffold. The resulting changes in microstructure can lead to a reduction in the area of contact between the matrix and the piezoelectric component which would lead to less efficient transfer of strain and eventually less piezoelectric output. In addition, microcracks or debonding at the interface can lead to stress concentrations causing inadequate mechanical coupling and hence degradation of the structure [92,93].

Nevertheless, degradation does not necessarily result in complete loss of electromechanical function. Functional performance may be maintained during the healing process if a controlled degradation profile is matched with bone regeneration. Over time, the scaffold will resorb and the new ECM, mineralized tissue and mature bone will take the load that the scaffold was once handling. This biological replacement can restore mechanical continuity and be able to transmit the physiological strain to the remaining piezoelectric components. Therefore, the rate of degradation of the scaffold is not the only factor involved in sustained electrical stimulation, but also on the balance of degradation rate and tissue regeneration rate [94-96].

This relationship shows how important it is to optimize degradation kinetics, and not just to maximize biodegradability. Porosity control of scaffolds, optimization of the magnesium phosphate composition, polymer reinforcement, mineralization of the scaffold surface and incorporation of bioactive coatings may help to slow the rate of structural collapse without compromising mechanical properties, thereby enabling efficient strain transfer in the scaffold. Similarly, the development of hierarchical porous structures that allow cells to infiltrate the structure, but not compromise its stiffness, may help maintain the electromechanical function throughout the intermediate stages of degradation [97,98].

Interfacial coupling between magnesium phosphate cement matrices and piezoelectric fillers

The electromechanical response of composite bone scaffolds is highly dependent on the interface between the magnesium phosphate cement matrix and embedded piezoelectric phase. The piezoelectric fillers, like barium titanate ($BaTiO_3$), zinc oxide (ZnO), poly(vinylidene fluoride) (PVDF) and piezoelectric ceramics without lead, only produce an electrical signal if they are subjected to a sufficiently large mechanical deformation [99]. Thus it is crucial that the surrounding magnesium phosphate matrix is able to transmit the physiological loading to the piezoelectric fillers at a mechanically stable interface [100].

The intimate physical contact and load transfer in an ideal matrix–filler interface enables externally applied compressive or cyclic forces to deform the piezoelectric phase uniformly. On the contrary, if there is inadequate adhesion between the particles, or poor dispersion of the fillers, debonding of the particles, slippage between the particles, stress concentration, and crack initiation can occur. Such faults limit mechanical strain reaching the piezoelectric fillers and so limit the electrical output even though the material itself has a piezoelectric effect. Moreover, degradation at the interface during scaffold resorption can gradually compromise the stress transfer, thereby compromising the long term electromechanical function [101,102].

A number of material design schemes have been suggested to maximize the interfacial coupling. Surface functionalization of ceramic piezoelectric particles with bioactive coatings, polymer interlayer or silane coupling agents can enhance the chemical compatibility and interface bonding with the magnesium phosphate matrix [103]. Uniform dispersion of piezoelectric fillers throughout the cement matrix helps to reduce the tendency of particles to agglomerate and results in a uniform distribution of stress. Furthermore, particle size, aspect ratio and filler concentration optimisation will increase the effective contact area between the matrix and the piezoelectric phase, and hence the efficiency of the strain transfer. The same elastic modulus of the matrix and filler also helps to eliminate the stress discontinuities at the matrix-filler interface and prevent early mechanical failure under cyclic loading [100]. This interfacial engineering will be critical to ensure continuous electrical stimulation and further enhance the regenerative nature of magnesium phosphate–piezoelectric composite scaffolds during the process of bone healing.

Future Perspective

Combining magnesium phosphate with piezoelectric materials emerge as multifunctional scaffolds that are capable of providing structural support, as well as biochemical and electrical stimulation, for improved bone regeneration. Although there has been significant progress in material

design as well as biological evaluation, challenges still remain to optimize the degradation of the scaffold in conjunction with its mechanical stability and piezoelectric activity so that electrical stimulation can be delivered throughout the bone healing process.

The performance of these composite scaffolds is anticipated to further improve with fabrication technology advances. Specifically, 3D and 4D printing impart the capability to develop patient-specific implants with controlled pore architecture, tailored mechanical properties, and precise distribution of piezoelectric components. The addition of bioactive molecules, stem cells, or extracellular vesicles might enhance osteogenesis, angiogenesis and tissue integration for better regeneration. In addition, computational approaches, including artificial intelligence, and finite element modelling are tools that help optimize scaffold composition, predict degradation behaviour as well as assess electromechanical performance prior to experimentation. These approaches could speed up the development of materials while decreasing the time and costs for optimizing the scaffold.

In order to achieve clinical translation, extensive long-term preclinical studies are needed to assess the degradation behaviour, biological safety, mechanical reliability, and regenerative efficacy under physiologically relevant conditions. For regulatory approval and clinical application of electroceuticals, standardized fabrication procedures, reproducible testing protocols, and scalable manufacturing processes will also be essential. Advancements in these fields will enable the fabrication of clinically relevant magnesium phosphate–piezoelectric scaffolds, which will assist in healing complex bone defects.

Conclusion

Biomaterials based on magnesium phosphate (MgP) have gained great interest in bone tissue engineering because of their excellent biocompatibility, suitable mechanical properties, injectable nature and controlled biodegradation. The gradual release of Mg^{2+} ions stimulates osteoblast proliferation, differentiation, angiogenesis and new bone formation, while the degrading scaffold temporarily supports the regenerating tissue. At the same time, piezoelectric materials like $BaTiO_3$, ZnO, and poly(vinylidene fluoride) (PVDF) have gained much attention for their ability to produce electrical signals under physiological mechanical loads, which closely resemble the electromechanical responses of native bone, and thus have potential to improve cellular responses during bone repair.

Incorporating magnesium phosphate into piezoelectric materials provides a multifunctional scaffold that provides ionic bioactivity, structural support and is electrically self-stimulating, which results in a favourable microenvironment for bone regeneration. MgP controls the degradation process and provides osteogenic Mg^{2+} ions, whereas the piezoelectric phase transforms mechanical stimuli into local electrical signals that induce cell adhesion, osteogenic differentiation and ECM mineralisation. This synergistic approach could have important implications in the development of next generation smart bone grafts. Optimization of scaffold composition, degradation rate, electromechanical properties, and long-term in vivo testing should be pursued to improve the safety, functionality, and clinical translation for treating complex bone defects.

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