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Ion—modified optimization of smart scaffolds in bone tissue regeneration

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Bioactive glasses and Calcium Phosphate bioceramics have emerged as promising scaffold biomaterials for bone tissue engineering. These materials possess inherent osteoinductive properties that work to create a more suitable environment for bone tissue formation. Additionally, these scaffolds exhibit dissolution properties when submerged in physiological fluids *in vivo* and therefore can release different ions. Incorporating therapeutic ion-modifiers that have independently demonstrated their osteogenic favorability to these scaffolds can further increase environmental suitability. This review discusses the favorable properties of bioactive glasses and Calcium Phosphate bioceramics in the context of Bone Tissue Engineering as well as potential incorporable metal ion-modifiers.

KEYWORDS

smart scaffolds, bone tissue engineering, scaffold optimization, biomaterials, ion-doped modifiers, bioactive glass, extracellular matrix (ECM)

1 Introduction

Bone tissue engineering (BTE) is an emerging subsect of regenerative medicine that offers an alternative treatment to bone fractures and segmental defects—both of which pose as a notable source of patient morbidity. Current treatments comprise mostly of allografts or synthetic grafts, and are estimated at a staggering annual cost of $5 billion in the US alone (Perez et al., 2018). To circumvent the common limitations of graft rejection or infection, BTE has been continually explored as a novel method in tissue repair.

Current approaches to BTE typically use mesenchymal stem cells [MSCs] and specific bioactive molecules to develop and promote the formation of new bone tissue, a process otherwise known as osteogenesis. Tissues produced by BTE *must* be able to fully integrate with host bone while also performing native functions like locomotion, electrolyte maintenance, load-bearing etc (Amini et al., 2012). In recent years, different inorganic ions have been researched to have therapeutic effects and hold significance in bone tissue formation (Schatkoski et al., 2021). While still not fully understood, certain osteogenic properties have been validated and their incorporation with an ECM-like scaffold help promote bone repair and regeneration (Motamedian et al., 2015). Although exogenous scaffolds primarily provide mechanical support and nutrient perfusion, to be in a stable *in vivo* environment they must also mimic normal ECM cues that accurately modulate cell

Abbreviations: BTE, Bone tissue engineering; ECM, Extracellular Matrix; HCA, Hydroxycarbonate Apatite; MSC, Mesenchymal Stem Cell; BG, Bioactive Glass; HCA, Hydroxyl Carbonated Apatite; MBG, Mesoporous Bioactive Glass; CaP, Calcium Phosphate.

behavior (Echeverria Molina et al., 2021). Various methodologies have already been established to yield functional scaffolds; *further* osteogenic optimization must also focus on specific biomaterials targeting these properties.

"Smart" scaffolds in BTE are comprised to act as environmentally sensitive vehicles for different osteogenic biomolecules. They can exert stimulating effects on tissues to increase stem cell attachment, differentiation, and continued proliferation (Motamedian et al., 2015). Among researched biomaterials, Calcium phosphate (CaP) bioceramics have emerged as suitable for BTE due to their osteoinductive abilities and structural similarity to native bone (Wei et al., 2022). The abundance of CaP crystals in native bone indicates their favorable properties and has thus become a central focus of bioceramic development. Similarly, bioactive glasses [BGs] have also emerged as an extremely promising biomaterial and are able to rapidly form a continuous bond with host bone. This bond allows seeded MSCs and other proteins to begin integrating with the native bone environment.

Additionally, the smooth incorporation both biomaterials have with inorganic metal ions as a bioactive molecule favors their use further. These ions and their displayed properties are critical in establishing a stable environment. This study reviews the attributes of CaP bioceramics and bioactive glasses as a scaffold material for BTE and discusses different osteogenic properties of therapeutic ions to improve bioactivity.

2 Biomaterials of BTE smart scaffolds

2.1 Calcium phosphate bioceramics

"Bioceramics" is an umbrella term to encompass a vast range of biocompatible inorganic non-metallic materials (Brunello et al., 2020). They vary from inert ceramic oxides to resorbable materials that are replaced by tissue following a period of time. Bioceramics are under consideration as a scaffold material mainly due to their mechanical and load-bearing properties, which are important attributes for hard tissue engineering (bone, teeth, etc.). However, in recent years large strides have been made in the development of bioceramics possessing intrinsic osteoinductive properties (Ginebra et al., 2018).

In bone ECM, calcium phosphate crystals act as a mineral phase to reinforce a collagen fiber network (Ginebra et al., 2018). Many different CaPs have demonstrated their presence can trigger differentiation of osteoprogenitor cells and lead to bone formation (Ginebra et al., 2018). Moreover, CaP bioceramics partially dissolve *in vivo*, resulting in higher local calcium and phosphate ion concentrations. This property contributes to a better osteogenic capacity and has been established in studies since the 1990s (Daculsi et al., 1989; Klein et al., 1994; Eliaz and Metoki, 2017). This dissolution can also release other ion-modifiers present within the biomaterial.

The hierarchical porous structure of bone, ranging in size from 20 to 400 μm (Vallet-Regí et al., 2011), is necessary for proper cell adherence and proliferation; CaP bioceramics have traditionally been macroporous (~100 μm) to accommodate osteocytes and allow for bone tissue ingrowth. Recent studies conducted on scaffold porosity have demonstrated that an increase of pore volume and specific surface area may significantly accelerate bone formation by enhancing protein and cell adhesion (Eliaz and Metoki, 2017). Studies conducted on high porosity CaP particles have suggested that their pore distribution does enhance protein adsorption qualities (Li et al., 2008; Zhu et al., 2010).

Similar to increased porosity, cell adhesion is also influenced by the inherent surface properties of CaP bioceramics. Attributes like surface roughness, surface charge, and percent of crystallinity all play a role in cell attachment and can be modified with other derivatives (Samavedi et al., 2013; Poli et al., 2019). Surface roughness mainly influences attachment by the grain size of CaP crystallites and particle size (Samavedi et al., 2013). This roughness differs depending on bioceramic composition, but most provide a favorable environment for adhesion and continued proliferation.

Although numerous studies have been conducted to verify the advantageous nature of CaP bioceramics, its main problem limiting clinical applications originate from its poor mechanical properties. CaP crystals are commonly characterized as brittle and possess relatively low tensile strength (Ambard and Mueninghoff, 2006). This incurs significant limitations of bone tissue grafts, where mechanical properties are of the utmost importance. Because of this, steps have been taken to try to adjust certain mechanical features. One strategy is to explore the development of composite materials with contrasting ratios of bioceramics and polymers (Brunello et al., 2020). Preliminary studies using polymers like polyethers and ketones, or acids like PLGA have shown to increase load bearing capacity and strain, but more research needs to be conducted for definitive conclusions to be stated (Zong et al., 2014; Yu H. et al., 2018). Once an optimized CaP bioceramic material is created, normal scaffolding methodologies can be used, substituting the CaP bioceramic as the main biomaterial.

2.2 Bioactive glass

Like bioceramics, bioactive glasses are an extremely attractive material for BTE due to their ability to attach to bone and induce bone formation. These materials are categorized as silicate-based materials with a Si-O-Si bonding network compatible with human tissue. With the addition of different ion modifiers, new derivatives of the Si-O-Si network can be constructed (Jones et al., 2010). A unique property of BGs allows for the release of various metallic ions from its glass structure, and with this researchers can obtain favored biological effects from tissue samples (Kargozar et al., 2019; Westhauser et al., 2020a). These ionic dissolution products permeate the native bone environment and affect osteoinductive ability, seemingly upregulating multiple gene families associated with bone production *in vivo* (Crush et al., 2021).

The osteogenic properties of BGs and their ability to release significant amounts of ions into the surrounding medium is a result of their inherent atomic structure. When submerged in physiological fluids present in the body, BGs become partially soluble (Vallet-Regi and Salinas, 2021). This causes an ionic exchange between BG material and protons in the solution, forming hydroxyl groups as a product (Crush et al., 2021). Further ion exchange also releases silicon from the BG and leads to the formation of a preliminary silica gel layer. Incorporation of hydroxyl groups and carbonate groups atop

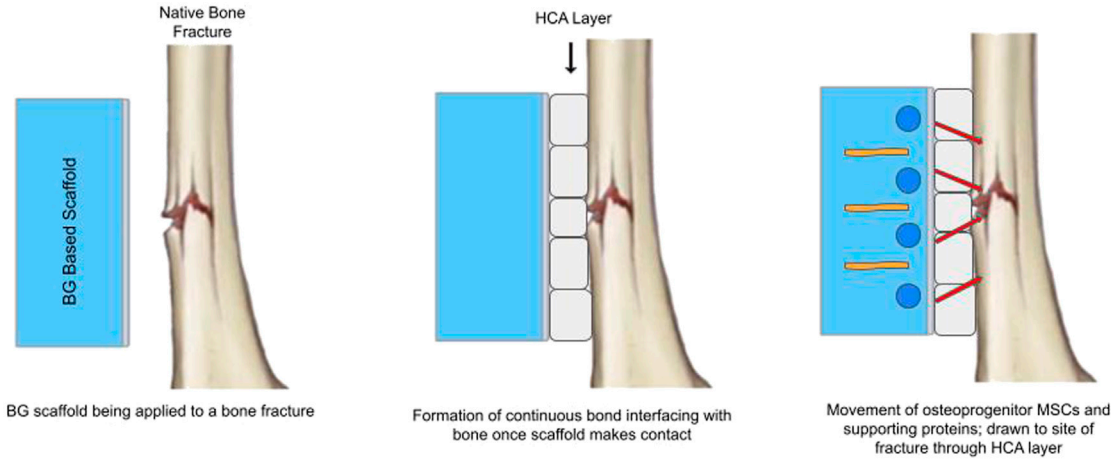

FIGURE 1
Simplified schematic of Bioactive Glass establishing continuous HCA bond, allowing for bioactive modifier and osteoprogenitor stem cell interfacing.

the silica gel layer creates a hydroxyl carbonated apatite [HCA] layer (Crush et al., 2021). This biologically compatible layer establishes as a continuous bond and rapidly interfaces with living bone *in vivo* (Yu Y. et al., 2018). Proteins and osteoprogenitor MSCs within the BG scaffold are drawn to the bone surface after the formation of the HCA layer, and start to integrate with native bone (Crush et al., 2021). This process is highlighted below in Figure 1.

Although preliminary bioactive glasses displayed improved bioactivity, its chemical/structural limitations and crystallization tendencies oftentimes prevent viable BTE scaffolds from being fabricated. Factors like temperature and viscosity range may break certain bonds in the glass network and allow it to rearrange to a weaker crystalline structure (Arstila et al., 2007). Like CaP bioceramics, BGs tend to display weak mechanical and stress bearing properties. To accommodate native bones' requirement of increased porosity, mesoporous bioactive glasses [MBGs] have recently garnered much attention. MBGs possess a similar composition to traditional BGs and can still be modified into different derivatives by ion substitution processes. However, their highly ordered mesoporous structure and high pore volume allow them to display unique structural characteristics, further improving biocompatibility and presenting great potential for future applications (Zhang et al., 2016; Wang et al., 2019). In addition, different fabrication techniques can affect the mechanical properties of MBGs; novel 3-D printing methods have shown to increase the mechanical strength of MBG scaffolds by almost 200 fold (Wu and Chang, 2012).

3 Various osteogenic inorganic-ion modifiers

Ion-functionalized scaffolds are composed of ion-doped (ion-modified) materials conducive to bone tissue regeneration. Incorporating different ion-doped bioceramic or BG materials in a novel scaffold may enhance an osteoinductive and stable environment for tissue proliferation. Current ions being researched presently were discovered at a higher concentration in native bone tissue or in localized trace elements observed *in vivo*. The effects of some ions are more known, while others are still under observation.

3.1 Calcium

Many different bioactive metal ions have been tested in the context of bone repair, with calcium being a prime example (Jiang et al., 2021). Being a core component of CaP bioceramics, its osteoinductive properties have been studied extensively. As the most abundant mineral in the body, it has a well-defined critical role; its extracellular presence is detected by the calcium sensing receptor (CaSR) and serves as a stimulus for differentiating MAPK signaling pathways (González-Vázquez et al., 2014). CaSR is a G-protein coupled receptor whose expression in osteoblasts plays a vital role in cell regulation (Ye et al., 2016); an increased concentration of Ca^{2+} ions significantly promotes osteogenic differentiation and bone marrow stem cell proliferation (Ye et al., 2016; Jiang et al., 2021). Multiple *in vitro* studies demonstrate that calcium loading into scaffolds encourages osteoinduction in MSCs (Motamedian et al., 2015; Aquino-Martínez et al., 2017; Lim et al., 2017; Lee et al., 2018).

3.2 Silver

Silver ions are known for antibacterial properties and have been shown to inhibit bacterial growth when released as a dissolution product (Hoppe et al., 2011). In a recent study conducted employing a rabbit model, preparation of a 3D-porous composite scaffold utilizing Ag^{+} ions was shown to have effectively eliminated bacterial infection and inhibit biofilm formation while still promoting bone repair (Weng et al., 2020). Furthermore, additional studies conducted using silver nanoparticles show significant enhancement of bone cell mineralization and differentiation (Deng et al., 2018; Qing et al., 2018). This indicates minimal interference with osteogenesis markers, and thus harbors a strong future potential for the use of silver as an antibacterial agent.

TABLE 1 Summary of Biological Effects of other Common Inorganic Ions for BTE.

Therapeutic ion	Biological response *in vivo/in vitro*	References
Boron	- Boron treatment of osteoprogenitor cells showed upregulation of bone formation marker genes	Fu et al. (2010), Lepry et al. (2017), O'Neill et al. (2018)
	- Moderate concentrations stimulate bone formation *in vitro*	
Calcium	- Calcium treatment of scaffolds encourages MSC osteoinduction	González-Vázquez et al. (2014), Ye et al. (2016), Aquino-Martínez et al. (2017), Lim et al. (2017), Lee et al. (2018), O'Neill et al. (2018), Jiang et al. (2021)
	- Extracellular presence detected by CaSR receptor and is a stimulus for MAPK pathway	
	- Increased calcium concentration promotes bone marrow stem cell proliferation and osteogenic differentiation	
Cobalt	- Promotes gene expression of growth factors that induce vascularization in bone tissue—critical component of bone formation	Drynda et al. (2018), O'Neill et al. (2018), Perni et al. (2018)
	- Generally kindles osteolytic and cytotoxic effects on osteoblasts which reduce proliferation	
Copper	- Promotes bone formation and mineralization	Hoppe et al. (2011), Dang et al. (2018), Foroutan et al. (2019), Bernhardt et al. (2021)
	- Common enzyme cofactor that induces collagen fibril cross-linking	
	- Induces MSC differentiation towards osteogenic lineage	
Magnesium	- Increased osteoblast proliferation and differentiation	Hoppe et al. (2011), He et al. (2016), Choi et al. (2020)
	- Plays important role in regulating signal transmission; regulates bone differentiation, development, remodeling	
Manganese	- Contradictory findings of biological response	Barrioni et al. (2019a), Barrioni et al. (2019b), Westhauser et al. (2020b), Prasadh et al. (2022)
	- When added in cell culture settings, improved ECM formation and upregulation of osteogenic marker genes	
	- Additional reports of inhibitory effects on stem cell differentiation and ECM protein synthesis	
Phosphorous	- Enhances cell proliferation and mineralization via ERK1/2 MAP kinase pathway	Beck et al. (2000), Ali Akbari Ghavimi et al. (2018), O'Neill et al. (2018)
	- Important signaling molecule for osteopontin gene expression: important protein to facilitate osteoblast attachment to ECM	
	- Possesses antibacterial properties	
Silver	- Possess antibacterial effects when released as a dissolution product	Hoppe et al. (2011), Deng et al. (2018), Qing et al. (2018), Weng et al. (2020)
	- Silver nanoparticle use can significantly enhance bone cell mineralization and differentiation	
Strontium	- Can be substituted in place of calcium in some regions of bone mineral	Yang et al. (2011), Fredholm et al. (2012), Hoppe et al. (2014), Bellucci et al. (2018), O'Neill et al. (2018), Kargozar et al. (2019)
	- Can upregulate certain osteoblast marker genes to enhance osteogenic differentiation while also inhibiting osteoclast activity	
Vanadium	- Can mimic effects of certain growth factors	O'Neill et al. (2018), Li et al. (2021a), Li et al. (2021b)
	- Higher concentrations found in bone tissue, indicating a role	
	In bone formation and homeostasis	
	- Low doses speculated to signal MAPK and ERK pathways, both of which are involved in osteoblast function	
	- May affect mesostructure and mechanical properties of modified BGs	
Zinc	- Essential trace element for skeletal growth	Lim et al. (2017), Deng et al. (2018), O'Neill et al. (2018), Neščáková et al. (2019)
	- Help enhance osteogenesis by inducing collagen synthesis and bone mineralization	
	- Supports osteogenic activity while simultaneously suppressing osteoclast activity	
	- Antioxidant and inflammatory agent and also provides anti-bacterial activity	

3.3 Strontium

Due to its physical and chemical properties similar to calcium, strontium has been widely researched in relation to bone regeneration. In osteoporosis, a strontium based drug derivative has been commonly used for treatment; this element can be substituted *in lieu* of calcium in certain regions of bone mineral (Kargozar et al., 2019). By upregulating osteoblast marker genes, strontium itself has shown to enhance osteogenic differentiation while also inhibiting osteoclast activity (Yang et al., 2011; O'Neill et al., 2018). Several iterations of BGs and CaP bioceramics have been developed where calcium is partially substituted with strontium, and most studies conclude a greater osteoconductive effect on new bone formation (Kargozar et al., 2019; Fredholm et al., 2012; Hoppe et al., 2014; Bellucci et al., 2018). However, this substitution does little to change the poor mechanical properties of these biomaterials and is a separate concern that still needs to be addressed.

3.4 Zinc

Zinc ions are an essential trace element required for normal skeletal growth; its ability to induce collagen synthesis and bone mineralization notably help enhance osteogenesis and has been demonstrated *in vitro* using fibrous scaffolds (Yang et al., 2011; Lim et al., 2017; Deng et al., 2018). Like strontium it helps support osteogenic activity while also simultaneously suppressing osteoclast activity (O'Neill et al., 2018). Additionally, like silver zinc is able to provide anti-bacterial activity and is also recognized as an antioxidant and inflammatory agent (O'Neill et al., 2018; Neščáková et al., 2019). Direct effects of zinc on bone cells are still not completely understood, yet its substantial impact in relation to bone growth have prompted future avenues of research employing Zn-containing BGs and bioceramics.

3.5 Other ions

Many more ions have been subject to extensive scientific examination in the context of BTE. In a microenvironment as complex as native bone tissue, an abundance of ions is of little surprise. However, research is still being conducted on the most impactful ions that would best be incorporated into a functional scaffold. Table 1 summarizes the biological responses of other common inorganic ions currently being explored in the context of BTE. Notably, many of these ions have only been explored preliminarily to identify their effect on osteogenic activity and no definitive conclusions with modified scaffolds have been made yet. The possibility of heavy metal poisoning with different ion concentrations is one significant concern that still needs proper evaluation, along with others. Because of these concerns and also due to the preliminary stage the research is in, most studies have been done in an *in vitro* environment.

4 Conclusion and future perspectives

In the pursuit of an optimized scaffold for bone tissue regeneration, many of these ion-doped materials could serve as an addition to a novel scaffold to further promote a stable osteogenic environment. Recent experiments over the last decade have successfully created distinct ion doped BGs and CaP bioceramics as scaffold materials. Many of these were created using existing fabrication techniques that facilitate ion deposition onto the surface of the biomaterial. Depending on the specific ion used and its effect on osteogenesis, different optimization properties were observed. Although current studies are still in preliminary stages, the osteogenic potential demonstrated using inorganic ions strongly indicate its future potential and various clinical applications.

Multiple future directions of research are available to translate these *in vitro* results into functional scaffolds capable of supporting grafts for clinical use. Primarily, biomaterial enhancement with polymer-based materials needs to be investigated more thoroughly. Although BGs and CaP bioceramics have proven to be a bone conducive scaffold material, severe mechanical and structural limitations prevent them from ever becoming a truly functional bone tissue scaffold. Identifying directions of structural enhancement can help change their inherent mechanical properties and increase stress bearing capabilities.

Additionally, the use of biomaterials with multiple functional ion-modifiers characterizes a promising direction for research. Current scaffolds have only utilized one ion at a time to generate osteoinductive effects. An ideal scaffold would incorporate multiple therapeutic ions, with each modifier factoring their own unique properties. Multiple ion modifiers would also better mimic the bone microenvironment and increase the overall functionality of the scaffold. Once a suitable scaffold has been created, the next step is to resolve the long-term direct effects of ions. This can be studied upon *in vivo* animal implantation with a functional scaffold to ensure the safety of inorganic metal ions in long-term grafts. While the prospect of fabricating a fully optimized scaffold for BTE may seem far-fetched, the promise of so many potential avenues of research present it as an attainable goal that scientists around the world can set their sights on.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Ali Akbari Ghavimi, S., Allen, B. N., Stromsdorfer, J. L., Kramer, J. S., Li, X., and Ulery, B. D. (2018). Calcium and phosphate ions as simple signaling molecules with versatile osteoinductivity. *Biomed. Mat.* 13, 055005. doi:10.1088/1748-605x/aac7a5

Ambard, A. J., and Mueninghoff, L. (2006). Calcium phosphate cement: review of mechanical and biological properties. *J. Prosthodont.* 15, 321–328. doi:10.1111/j.1532-849x.2006.00129.x

Amini, A. R., Laurencin, C. T., and Nukavarapu, S. P. (2012). Bone tissue engineering: recent advances and challenges. *Crit. Rev. Biomed. Eng.* 40, 363–408. doi:10.1615/critrevbiomedeng.v40.i5.10

Aquino-Martínez, R., Angelo, A. P., and Pujol, F. V. (2017). Calcium-containing scaffolds induce bone regeneration by regulating mesenchymal stem cell differentiation and migration. *Stem Cell Res. Ther.* 8, 265. doi:10.1186/s13287-017-0713-0

Arstila, H., Vedel, E., Hupa, L., and Hupa, M. (2007). Factors affecting crystallization of bioactive glasses. *J. Eur. Ceram. Soc.* 27, 1543–1546. doi:10.1016/j.jeurceramsoc.2006.04.017

Barrioni, B. R., Naruphontjirakul, P., Norris, E., Li, S., Kelly, N. L., Hanna, J. V., et al. (2019a). Effects of manganese incorporation on the morphology, structure and cytotoxicity of spherical bioactive glass nanoparticles. *J. Colloid Interface Sci.* 547, 382–392. doi:10.1016/j.jcis.2019.04.016

Barrioni, B. R., Norris, E., Li, S., Naruphontjirakul, P., Jones, J. R., and Pereira, M. de M. (2019b). Osteogenic potential of sol–gel bioactive glasses containing manganese. *J. Mat. Sci. Mat. Med.* 30, 86. doi:10.1007/s10856-019-6288-9

Beck, G. R., Zerler, B., and Moran, E. (2000). Phosphate is a specific signal for induction of osteopontin gene expression. *Proc. Natl. Acad. Sci.* 97, 8352–8357. doi:10.1073/pnas.140021997

Bellucci, D., Cannillo, V., Anesi, A., Salvatori, R., Chiarini, L., Manfredini, T., et al. (2018). Bone regeneration by novel bioactive glasses containing strontium and/or magnesium: A preliminary *in-vivo* study. *Materials* 11, 2223. doi:10.3390/ma11112223

Bernhardt, A., Bacova, J., Gbureck, U., and Gelinsky, M. (2021). Influence of Cu2+ on osteoclast formation and activity *in vitro*. *Int. J. Mol. Sci.* 22, 2451. doi:10.3390/ijms22052451

Brunello, G., Panda, S., Schiavon, L., Sivolella, S., Biasetto, L., and Del Fabbro, M. (2020). The impact of bioceramic scaffolds on bone regeneration in preclinical *in vivo* studies: A systematic review. *Materials* 13, 1500. doi:10.3390/ma13071500

Choi, S., Kim, K.-J., Cheon, S., Kim, E.-M., Kim, Y.-A., Park, C., et al. (2020). Biochemical activity of magnesium ions on human osteoblast migration. *Biochem. Biophys. Res. Commun.* 531, 588–594. doi:10.1016/j.bbrc.2020.07.057

Crush, J., Hussain, A., Seah, K. T. M., and Khan, W. S. (2021). Bioactive glass: methods for assessing angiogenesis and osteogenesis. *Front. Cell Dev. Biol.* 9, 643781. doi:10.3389/fcell.2021.643781

Daculsi, G., Legeros, R. Z., Nery, E., Lynch, K., and Kerebel, B. (1989). Transformation of biphasic calcium phosphate ceramics*in vivo*: ultrastructural and physicochemical characterization. *J. Biomed. Mat. Res.* 23, 883–894. doi:10.1002/jbm.820230806

Dang, W., Li, T., Li, B., Ma, H., Zhai, D., Wang, X., et al. (2018). A bifunctional scaffold with CuFeSe2 nanocrystals for tumor therapy and bone reconstruction. *Biomaterials* 160, 92–106. doi:10.1016/j.biomaterials.2017.11.020

Deng, Y., Yang, L., Huang, X., Chen, J., Shi, X., Yang, W., et al. (2018). Dual Ag/ZnO-decorated micro-/nanoporous sulfonated polyetheretherketone with superior antibacterial capability and biocompatibility via layer-by-layer self-assembly strategy. *Macromol. Biosci.* 18, 1800028. doi:10.1002/mabi.201800028

Drynda, A., Drynda, S., Kekow, J., Lohmann, C. H., and Bertrand, J. (2018). Differential effect of cobalt and chromium ions as well as CoCr particles on the expression of osteogenic markers and osteoblast function. *Int. J. Mol. Sci.* 19, 3034. doi:10.3390/ijms19103034

Echeverria Molina, M. I., Malollari, K. G., and Komvopoulos, K. (2021). Design challenges in polymeric scaffolds for tissue engineering. *Front. Bioeng. Biotechnol.* 9, 617141. doi:10.3389/fbioe.2021.617141

Eliaz, N., and Metoki, N. (2017). Calcium phosphate bioceramics: A review of their history, structure, properties, coating technologies and biomedical applications. *Materials* 10, 334. doi:10.3390/ma10040334

Foroutan, F., McGuire, J., Gupta, P., Nikolaou, A., Kyffin, B. A., Kelly, N. L., et al. (2019). Antibacterial copper-doped calcium phosphate glasses for bone tissue regeneration. *ACS Biomater. Sci. Eng.* 5, 6054–6062. doi:10.1021/acsbiomaterials.9b01291

Fredholm, Y. C., Karpukhina, N., Brauer, D. S., Jones, J. R., Law, R. V., and Hill, R. G. (2012). Influence of strontium for calcium substitution in bioactive glasses on degradation, ion release and apatite formation. *J. R. Soc. Interface.* 9, 880–889. doi:10.1098/rsif.2011.0387

Fu, Q., Rahaman, M. N., Fu, H., and Liu, X. (2010). Silicate, borosilicate, and borate bioactive glass scaffolds with controllable degradation rate for bone tissue engineering applications. I. Preparation and *in vitro* degradation. *J. Biomed. Mat. Res. A* 95A, 164–171. doi:10.1002/jbm.a.32824

Ginebra, M.-P., Espanol, M., Maazouz, Y., Bergez, V., and Pastorino, D. (2018). Bioceramics and bone healing. *EFORT Open Rev.* 3, 173–183. doi:10.1302/2058-5241.3.170056

González-Vázquez, A., Planell, J. A., and Engel, E. (2014). Extracellular calcium and CaSR drive osteoinduction in mesenchymal stromal cells. *Acta Biomater.* 10, 2824–2833. doi:10.1016/j.actbio.2014.02.004

He, L. Y., Zhang, X. M., Liu, B., Tian, Y., and Ma, W. H. (2016). Effect of magnesium ion on human osteoblast activity. *Braz. J. Med. Biol. Res. Rev. Bras. Pesqui. Medicas E Biol.* 49, e5257–S0100. doi:10.1590/1414-431x20165257

Hoppe, A., Güldal, N. S., and Boccaccini, A. R. (2011). A review of the biological response to ionic dissolution products from bioactive glasses and glass-ceramics. *Biomaterials* 32, 2757–2774. doi:10.1016/j.biomaterials.2011.01.004

Hoppe, A., Sarker, B., Detsch, R., Hild, N., Mohn, D., Stark, W. J., et al. (2014). *In vitro* reactivity of Sr-containing bioactive glass (type 1393) nanoparticles. *J. Non-Cryst. Solids.* 387, 41–46. doi:10.1016/j.jnoncrysol.2013.12.010

Jiang, S., Wang, M., and He, J. (2021). A review of biomimetic scaffolds for bone regeneration: toward a cell-free strategy. *Bioeng. Transl. Med.* 6, e10206. doi:10.1002/btm2.10206

Jones, J. R., Lin, S., Yue, S., Lee, P. D., Hanna, J. V., Smith, M. E., et al. (2010). Bioactive glass scaffolds for bone regeneration and their hierarchical characterisation. *Proc. Inst. Mech. Eng. H.* 224, 1373–1387. doi:10.1243/09544119jeim836

Kargozar, S., Montazerian, M., Fiume, E., and Baino, F. (2019). Multiple and promising applications of strontium (Sr)-Containing bioactive glasses in bone tissue engineering. *Front. Bioeng. Biotechnol.* 7, 161. doi:10.3389/fbioe.2019.00161

Klein, C., de Groot, K., Chen, W., Li, Y., and Zhang, X. (1994). Osseous substance formation induced in porous calcium phosphate ceramics in soft tissues. *Biomaterials* 15, 31–34. doi:10.1016/0142-9612(94)90193-7

Lee, M. N., Hwang, H.-S., Oh, S.-H., Roshanzadeh, A., Kim, J.-W., Song, J. H., et al. (2018). Elevated extracellular calcium ions promote proliferation and migration of mesenchymal stem cells via increasing osteopontin expression. *Exp. Mol. Med.* 50, 1–16. doi:10.1038/s12276-018-0170-6

Lepry, W. C., Naseri, S., and Nazhat, S. N. (2017). Effect of processing parameters on textural and bioactive properties of sol–gel-derived borate glasses. *J. Mat. Sci.* 52, 8973–8985. doi:10.1007/s10853-017-0968-y

Li, J., Li, J., Wei, Y., Xu, N., Li, J., Pu, X., et al. (2021a). Ion release behavior of vanadium-doped mesoporous bioactive glass particles and the effect of the released ions on osteogenic differentiation of BMSCs *via* the FAK/MAPK signaling pathway. *J. Mat. Chem. B* 9, 7848–7865. doi:10.1039/d1tb01479j

Li, J., Li, X., Li, J., Pu, X., Wang, J., Huang, Z., et al. (2021b). Effects of incorporated vanadium and its chemical states on morphology and mesostructure of mesoporous bioactive glass particles. *Microporous Mesoporous Mater* 319, 111061. doi:10.1016/j.micromeso.2021.111061

Li, X., van Blitterswijk, C. A., Feng, Q., Cui, F., and Watari, F. (2008). The effect of calcium phosphate microstructure on bone-related cells *in vitro*. *Biomaterials* 29, 3306–3316. doi:10.1016/j.biomaterials.2008.04.039

Lim, S. S., Chai, C. Y., and Loh, H.-S. (2017). *In vitro* evaluation of osteoblast adhesion, proliferation and differentiation on chitosan-TiO2 nanotubes scaffolds with Ca2+ ions. *Mat. Sci. Eng. C* 76, 144–152. doi:10.1016/j.msec.2017.03.075

Motamedian, S. R., Hosseinpour, S., Ahsaie, M. G., and Khojasteh, A. (2015). Smart scaffolds in bone tissue engineering: A systematic review of literature. *World J. Stem cells.* 7, 657–668. doi:10.4252/wjsc.v7.i3.657

Neščáková, Z., Zheng, K., Liverani, L., Nawaz, Q., Galusková, D., Kaňková, H., et al. (2019). Multifunctional zinc ion doped sol – gel derived mesoporous bioactive glass nanoparticles for biomedical applications. *Bioact. Mat.* 4, 312–321. doi:10.1016/j.bioactmat.2019.10.002

O'Neill, E., Awale, G., Daneshmandi, L., Umerah, O., and Lo, K. W.-H. (2018). The roles of ions on bone regeneration. *Drug Discov. Today.* 23, 879–890. doi:10.1016/j.drudis.2018.01.049

Perez, J. R., Kouroupis, D., Li, D. J., Best, T. M., Kaplan, L., and Correa, D. (2018). Tissue engineering and cell-based Therapies for fractures and bone defects. *Front. Bioeng. Biotechnol.* 6, 105. doi:10.3389/fbioe.2018.00105

Perni, S., Yang, L., Preedy, E. C., and Prokopovich, P. (2018). Cobalt and Titanium nanoparticles influence on human osteoblast mitochondrial activity and biophysical properties of their cytoskeleton. *J. Colloid Interface Sci.* 531, 410–420. doi:10.1016/j.jcis.2018.07.028

Poli, E., Magnaudeix, A., Damia, C., Lalloué, F., Chaleix, V., Champion, E., et al. (2019). Advanced protocol to functionalize CaP bioceramic surface with peptide sequences and effect on murine pre-osteoblast cells proliferation. *Bioorg. Med. Chem. Lett.* 29, 1069–1073. doi:10.1016/j.bmcl.2019.03.002

Prasadh, S., Gupta, M., and Wong, R. (2022). *In vitro* cytotoxicity and osteogenic potential of quaternary Mg-2Zn-1Ca/X-Mn alloys for craniofacial reconstruction. *Sci. Rep.* 12, 8259. doi:10.1038/s41598-022-12490-0

Qing, T., Mahmood, M., Zheng, Y., Biris, A. S., Shi, L., and Casciano, D. A. (2018). A genomic characterization of the influence of silver nanoparticles on bone differentiation in MC3T3-E1 cells. *J. Appl. Toxicol.* 38, 172–179. doi:10.1002/jat.3528

Samavedi, S., Whittington, A. R., and Goldstein, A. S. (2013). Calcium phosphate ceramics in bone tissue engineering: A review of properties and their influence on cell behavior. *Acta Biomater.* 9, 8037–8045. doi:10.1016/j.actbio.2013.06.014

Schatkoski, V. M., Larissa do Amaral Montanheiro, T., Canuto de Menezes, B. R., Pereira, R. M., Rodrigues, K. F., Ribas, R. G., et al. (2021). Current advances concerning the most cited metal ions doped bioceramics and silicate-based bioactive glasses for bone tissue engineering. *Ceram. Int.* 47, 2999–3012. doi:10.1016/j.ceramint.2020.09.213

Tang, G., Liu, Z., Liu, Y., Yu, J., Wang, X., Tan, Z., et al. (2021). Recent trends in the development of bone regenerative biomaterials. *Front. Cell Dev. Biol.* 9, 665813. doi:10.3389/fcell.2021.665813

Vallet-Regí, M., and Ruiz-Hernández, E. (2011). Bioceramics: from bone regeneration to cancer nanomedicine. *Adv. Mat.* 23, 5177–5218. doi:10.1002/adma.201101586

Vallet-Regi, M., and Salinas, A. J. (2021). Mesoporous bioactive glasses for regenerative medicine. *Mat. Today bio.* 11, 100121. doi:10.1016/j.mtbio.2021.100121

Wang, Y., Pan, H., and Chen, X. (2019). The preparation of hollow mesoporous bioglass nanoparticles with excellent drug delivery capacity for bone tissue regeneration. *Front. Chem.* 7, 283. doi:10.3389/fchem.2019.00283

Wei, H., Cui, J., Lin, K., Xie, J., and Wang, X. (2022). Recent advances in smart stimuli-responsive biomaterials for bone therapeutics and regeneration. *Bone Res.* 10, 17. doi:10.1038/s41413-021-00180-y

Weng, W., Li, X., Nie, W., Liu, H., Liu, S., Huang, J., et al. (2020). <p>One-Step preparation of an AgNP-nHA@RGO three-dimensional porous scaffold and its application in infected bone defect treatment</p>. *Int. J. Nanomedicine.* 15, 5027–5042. doi:10.2147/ijn.s241859

Westhauser, F., Hohenbild, F., Arango-Ospina, M., Schmitz, S. I., Wilkesmann, S., Hupa, L., et al. (2020a). Bioactive glass (BG) ICIE16 shows promising osteogenic properties compared to crystallized 45S5-BG. *Int. J. Mol. Sci.* 21, 1639. doi:10.3390/ijms21051639

Westhauser, F., Wilkesmann, S., Nawaz, Q., Schmitz, S. I., Moghaddam, A., and Boccaccini, A. R. (2020b). Osteogenic properties of manganese-doped mesoporous bioactive glass nanoparticles. *J. Biomed. Mat. Res. A* 108, 1806–1815. doi:10.1002/jbm.a.36945

Wu, C., and Chang, J. (2012). Mesoporous bioactive glasses: structure characteristics, drug/growth factor delivery and bone regeneration application. *Interface Focus* 2, 292–306. doi:10.1098/rsfs.2011.0121

Yang, F., Yang, D., Tu, J., Zheng, Q., Cai, L., and Wang, L. (2011). Strontium enhances osteogenic differentiation of mesenchymal stem cells and *in vivo* bone formation by activating wnt/catenin signaling. *Stem Cells* 29, 981–991. doi:10.1002/stem.646

Ye, J., Ai, W., Zhang, F., Zhu, X., Shu, G., Wang, L., et al. (2016). Enhanced proliferation of porcine bone marrow mesenchymal stem cells induced by extracellular calcium is associated with the activation of the calcium-sensing receptor and ERK signaling pathway. *Stem Cells Int.* 2016, 6570671–6570711. doi:10.1155/2016/6570671

Yu, H., Chen, Y., Mao, M., Liu, D., Ai, J., and Leng, W. (2018a). PEEK-biphasic bioceramic composites promote mandibular defect repair and upregulate BMP-2 expression in rabbits. *Mol. Med. Rep.* 17, 8221–8227. doi:10.3892/mmr.2018.8867

Yu, Y., Bacsik, Z., and Edén, M. (2018b). Contrasting *in vitro* apatite growth from bioactive glass surfaces with that of spontaneous precipitation. *Materials* 11, 1690. doi:10.3390/ma11091690

Zhang, X., Zeng, D., Li, N., Wen, J., Jiang, X., Liu, C., et al. (2016). Functionalized mesoporous bioactive glass scaffolds for enhanced bone tissue regeneration. *Sci. Rep.* 6, 19361. doi:10.1038/srep19361

Zhu, X. D., Zhang, H. J., Fan, H. S., Li, W., and Zhang, X. D. (2010). Effect of phase composition and microstructure of calcium phosphate ceramic particles on protein adsorption. *Acta Biomater.* 6, 1536–1541. doi:10.1016/j.actbio.2009.10.032

Zong, C., Qian, X., Tang, Z., Hu, Q., Chen, J., Gao, C., et al. (2014). Biocompatibility and bone-repairing effects: comparison between porous poly-lactic-Co-glycolic acid and nano-hydroxyapatite/poly(lactic acid) scaffolds. *J. Biomed. Nanotechnol.* 10, 1091–1104. doi:10.1166/jbn.2014.1696