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Review

Bioinorganics in Bioactive Calcium Silicate Ceramics for Bone Tissue Repair: Bioactivity and Biological Properties

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Abstract

Bioinorganics and the use of metal ions in the synthesis and design of new materials have received considerable attention with regard to use as new biomaterials. One of the important roles of metal ions is the control of dissolution in biomaterials, which has an influence on their biological and chemical properties. Up until now, metal ions such as magnesium (Mg), zinc (Zn), titanium (Ti) and zirconium (Zr) have been used to dope silicate- and phosphate-based ceramics. Calcium silicate ($CaSiO_3$, CS) ceramics are biocompatible and bioactive. Some CS ceramics have exhibited superior apatite formation ability in simulated body fluids (SBF) and their ionic dissolution products have been shown to enhance cell proliferation and differentiation. Their main drawback, however, is the high dissolution rate as this is detrimental to cells. Metal ions are used to modify their chemical composition and structure in order to overcome this complication. In this review paper, we consider the apatite formation ability, dissolution and the *in vitro* and *in vivo* biological properties of ion-doped CS ceramics such as bredigite, akermanite, monticellite, diopside, merwinite, hardystonite, baghdadite and sphene. Overall, according to the studies conducted on CS bioceramics, they may be a good candidate for bone tissue regeneration.

Keywords: Calcium silicate, chemical stability, ion doping

I. Introduction

In the early 1970s, Hench *et al.* developed a new class of bioactive materials based on SiO_2-CaO-Na_2O-P_2O_5 with high bioactivity for bone tissue engineering [1]. Inserting an inorganic component increases the bioactivity of materials [2,3]. Bioinorganics (the use of inorganic elements) to support bone formation can eradicate the side-effects and complications of hormones or growth factors [3,4]. As well as the physical conditions such as surface morphology, the chemical composition and ionic dissolution of the biomaterials are determinant with regard to cellular response and activity [5–7]. Two main characteristics of CS compared to calcium phosphate ceramics are excellent bioactivity and biodegradability. However, the main drawbacks of CS and CS-based scaffolds are weak mechanical strength and high degradation, which leads to an increased pH value in the environment that is lethal for cells [8]. In addition, the CS cannot support human bone cell proliferation [9]. In the 1990s, De Aza revealed that pure CS-induced *in vitro* bone-like apatite formations in simulated body fluids (SBF) contain inorganic ions similar to concentrations of human extracellular matrix (ECM) and bond with the host bone tissue *in vivo* [10]. A further study by Siriphannon *et al.* indicated that the apatite formation rate of CS is faster than that of bioactive glass in SBF [11]. In the past ten years, ion modification of CS ceramics has been utilized to improve their mechanical and biomedical properties. With the Ca-Si-X system (in which X could be Mg, Zn, Ti and Zr), potential materials have been found for bone tissue regeneration [7, 12–16]. These materials possess good osteoinductivity and osteoconductivity [17–19]. New classes of ion-doped bioactive CS with a wide range of compositions (these different compositions are prepared by means of doping with various ions) have been developed [20]. For this reason, the aim of this review is to investigate the *in vitro* and *in vivo* biological properties of ion-doped CS ceramics from a wide range of research papers.

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II. Different Ions used in Doping Bioceramics

Doping means the incorporation of elements (such as ions) into the material at a low concentration compared to the main constituent, usually to improve its properties. Foreign constituents in the material that do not come from a controlled process are defined as impurities. Dopants are useful to produce functional materials. Doping has certain influences on the material including the direct relationship between functionality and dopant, structural control and unanticipated effects on the structure morphology [21]. One important feature in different types of ion-doped biomaterials is their ability to release different ions (Fig. 1) [22,23]. Modifying the interfacial chemistry of biomaterials with molecules, atoms and ions is important in bone formation. The incorporation of different ions such as magnesium (Mg^{2+}), silicon (Si^{4+}), zinc (Zn^{2+}), strontium (Sr^{2+}), zirconium (Zr^{4+}) and titanium (Ti^{4+}) into the biomaterial structure enhances the integration of the implant with the bone tissue. Previous reports assumed that similar compositions and structural properties can be essential factors for apatite formation on the surface of ceramic, which can influence bioactivity (Fig. 2) [24,25]. Therefore, it is critical to find out how different biomaterials and their modifications might mediate the bone-associated gene expression and their proteins [26–28]. It is difficult to isolate the effect of a distinct constituent by means of the substitution of an ion element into the lattice structure of the ceramics, because not only the chemical composition but also many physico-chemical properties might change [29]. Divalent Zn and Sr ions are doped into CS ceramics owing to their beneficial effects on bone mineralization. Furthermore, tetravalent ion such as Ti and Zr have been incorporated into CS ceramics because they can form a network with Si, making the materials stable and decreasing ion release from the material [9]. The chemistry of such bioceramics is thus one of the most important aspects with regard to influencing the proliferation and differentiation of different cells [30]. One method to improve the physical and biological properties of CS ceramics is to introduce ions that modify their structure and chemical composition [31,32]. Introducing versatile kinds of metal ions into CS ceramics always leads to complicated structures and various bond strengths between ions, altering ion release [33,34]. Such complicated structures might change the stability and dissolution rate [35–37]. A high pH value and dissolution of Ca and Si ions prevent cell differentiation and growth, whereas low ion concentrations of Ca and Si and a suitable pH value stimulate osteoblast proliferation, differentiation and gene expression [36]. Ion-doped CS ceramics form new materials in which the crystal structure is different from that of CS with a decreased dissolution rate. In addition, the ion concentrations of Ca and Si and in turn the pH value of the surrounding culture media are lowered [57]. These novel materials possess a similar composition to CS with improved mechanical and biomedical properties [9]. In the following, we will categorize and discuss the effect of the incorporation of diverse ions in the structure of CS ceramics.

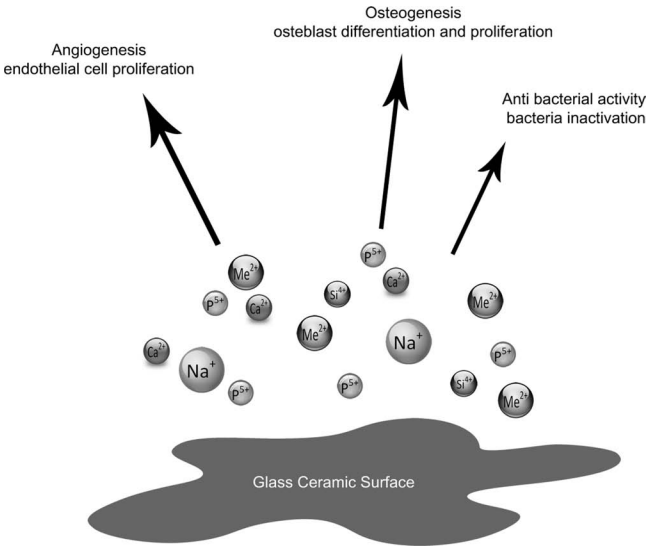

Fig. 1: Schematic showing the biological response to ionic dissolution products of ceramics and glass ceramics (Me^{2+} indicates metal ions such as Sr, Zn, Mg, etc.).

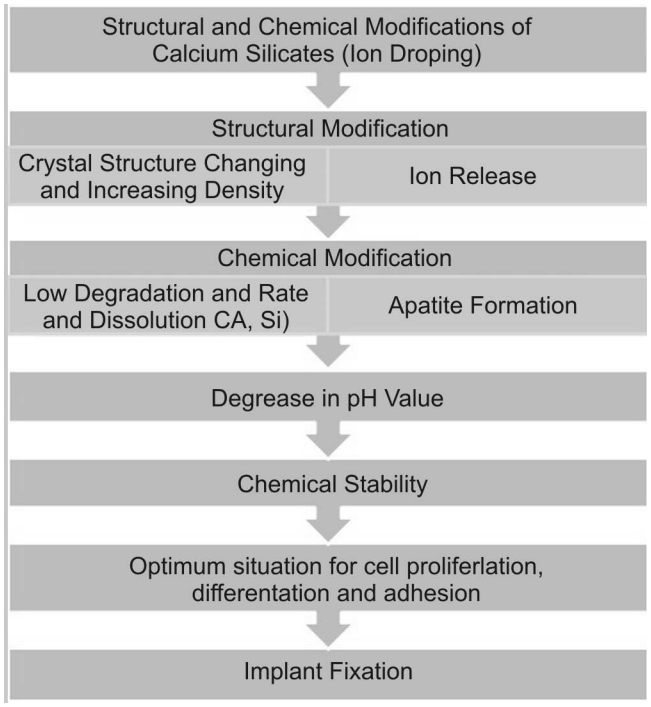

Fig. 2: Structural and chemical modifications of CS ceramics improving their biological and chemical properties.

(1) Magnesium

Mg is an important trace element in the body, including bone and extracellular matrix, which is closely related to cell differentiation, mineralization of calcined tissue and has an indirect effect on mineral metabolism [35,38–43]. Mg can enhance osteoblast (OB) adhesion and directly stimulate OB proliferation [39,41,44,45]. Mg deficiency in the body inhibits cellular growth and increases the risk of osteoporosis [42,46–48]. It is known that Mg plays a critical role in the biodegradation of ceramics. Mg also decreases the solubility of ceramics [36].

(2) Silicon

Previous studies have indicated that the mechanism of bioactivity is directly associated with the release of Si [13,49,50]. Low concentrations of Si have a stimulatory effect on OB proliferation, but high concentrations, i.e. 9.95 mM, have an inhibitory effect on cell proliferation [34,36]. Si contributes to the growth of bone tissue [51,52] and the bone mineralization process [53–56]. Si deficiency leads to abnormal bone formation [57]. Si enhances the bioactivity of ceramics *in vitro* and OB proliferation [58–61]. Si is tetravalent the same as Ti, ionically joining to Ca to enhance the stability of materials [62].

(3) Strontium

Another known bone seeker element in the body is Sr. Most of the strontium content is found in the skeleton; it has anabolic effects and is recommended for the treatment of osteoporosis [37,63]. Sr can enhance bone formation and reduce bone resorption [64–66]. It is suggested that Sr can be incorporated in the structure on a substitutional basis for Ca as their ionic radii are similar [67]. However, the atomic radius of Sr is larger than that of Ca, so that it occupies more space in the lattice and impedes the movement and release of the other ions and reduces the dissolution rate of CS ceramics [63,68]. Sr enhances the density, and the higher density causes lower ion degradation [69]. Furthermore, Sr influences ceramic dissolution based on grain structure and boundaries [70–72]. There are two mechanisms by which Sr is incorporated in the bone including surface exchange and ionic substitution [32]. In the first mechanism, Sr is incorporated into the crystal lattice of the bone mineral phase and in the second mechanism Sr is taken up through ionic exchange with Ca in the bone.

(4) Zinc

Another important element in the human body is Zn. Zn contributes to bone metabolism [73–78]. Zn deficiency leads to the retardation of bone growth in humans and animals [78,79]. The anti- inflammation of Zn has been demonstrated and Zn deficiency can induce delayed wound repair and immune dysfunction [80]. Zn can be used as reinforcement in CS ceramics [33]. Gross *et al.* reported that Zn influences the outer membrane of bacteria through structural modification and can cause cell death [81]. However, heavy metals react with proteins in the bacteria, which results in protein inactivation and consequently cell death [82,83].

(5) Calcium

One of the best known ions in the human body is Ca; it is distributed in the bone and extracellular fluids [84]. Calcium deficiency leads to bone metabolic diseases and osteoporosis [85–87]. Ca can regulate osteogenesis by establishing interaction between the OB and OC cell surface Ca-sensing receptors (CaSR) [84,88–92].

(6) Zirconium

Zr is employed extensively in prosthetic equipment on account of its good mechanical properties and biocompatibility [93,94]. Zr is tetravalent so it might be thought that the introduction of this ion into the CS structure could be helpful for its stability [7].

III. Chemical Stability, pH Value and Apatite Formation of CS Ceramics

Bioactive materials are generally able to bond directly with the bone and can be considered as bone-repairing materials in clinical applications [95]. There are two mechanisms for apatite formation on the surface of materials based on soaking in SBF. One is the release of some ions from the material that form a negative charge on the surface [23] and the other is a specific microstructure on micro- and nano-scale to provide nucleation sites [96]. In bone implant application CaO and SiO_2 are necessary for apatite formation [97–99]. The apatite layer must have low crystallinity and a composition similar to that of the bone mineral phase [100,101]. Bone-like apatite stimulates signalling proteins and cells to initiate a sequence of incidents that lead to bone formation. The HA layer grows via the reaction of the Ca, phosphate (PO_4^{3-}) and hydroxide (OH^-) ions and is sometimes integrated with carbonate anions (CO_3^{2-}) [102]. The higher rate of apatite layer formation is related to the higher dissolution rate of the surface [103]. The mechanism of apatite forming ability comprises several stages. First, calcium ions are released from the surface, in the next stage many silanol (Si-OH) groups are formed on the surface. These Si-OH groups make the apatite nucleation heterogeneous and Ca ions enhance ionic activity and apatite nucleation. When apatite nuclei are forming on the surface, they grow spontaneously using calcium phosphate (CaP) ions from the SBF (Fig. 3) [104]. The apatite forming ability in CS ceramics is mostly associated with high reactivity, which leads to the favourable release of Ca and a raised pH value in the SBF [4]. However, the biodegradation of wollastonite (basic compound of CS ceramics) is too fast [105]. Another factor that might affect the degradation property of ceramics is the structure [106,107]. Wollastonite has a triclinic structure [108]. The preliminary alkali ion exchange with hydrogen ions is the reason for the increase in the pH value in the surrounding environment. As a result, a hydrated silica layer is formed on the surface [109]. As time passes, the formed apatite layer becomes thicker owing to a decrease in phosphorous (P) concentrations to stabilize the pH value via inhibiting ion exchange [109,110]. The apatite forming ability in SBF and chemical stability are usually thought of as contradictory factors and obtaining both of them simultaneously is typically difficult [33]. Apatite formation ability is directly associated with the dissolution of materials and the rate of apatite formation decreases with the lowering of bioactive glass dissolution [107,111]. The pH value is one factor that inhibits cell proliferation. This parameter has multiple effects on cell metabolism and affects cell proliferation [36,111,112]. Bone remodelling depends on the pH value [113,114]. The high dissolution and degradation rate of CS ceramics result in an elevated pH value in the environment, indicating their chemical instability, which is lethal for cells and impedes cell growth [8]. So, their osseointegration ability is affected (Fig. 4). There are three routes to control the environmental pH of biomaterials including composition, ion doping (discussed in this paper) and surface modification [115].

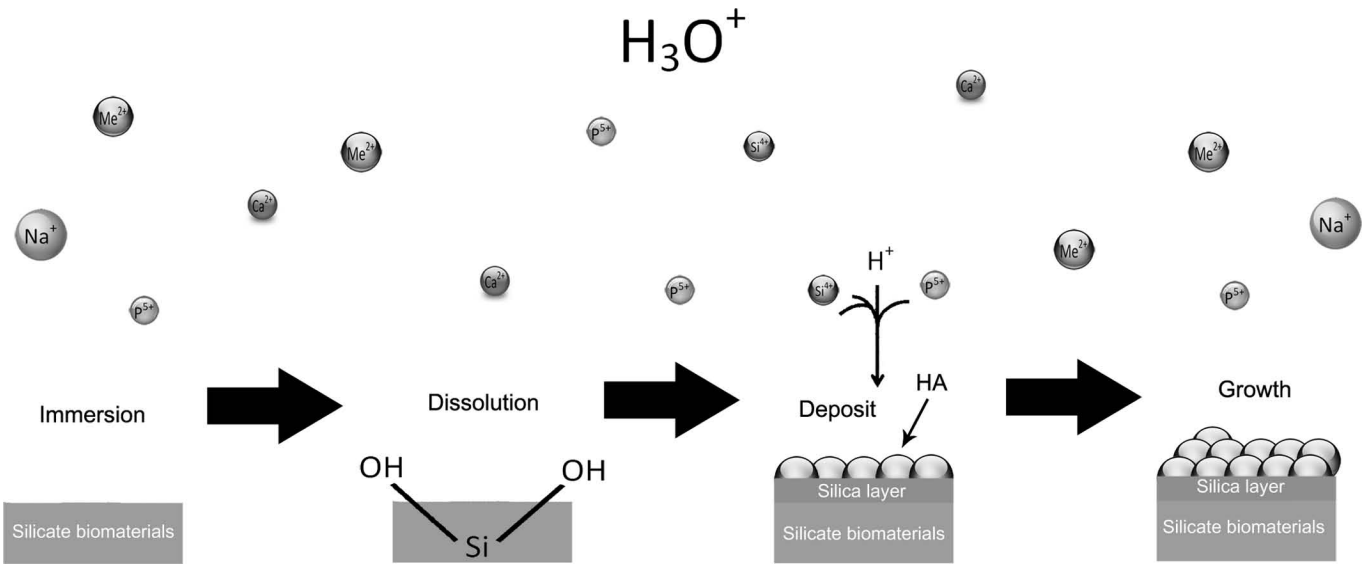

Fig. 3: Mechanism of apatite formation ability of CS ceramics.

Lin *et al.* reported that HA/wollastonite composite has an appropriate dissolution rate [116]. Zhao *et al.* showed that coated PLGA on the surface of a CS scaffold improves chemical stability [117]. It should be noted that bone is also known as biological apatite which is not pure HA and comprises Zn and Sr ions that can be replaced with different cations present in the structure of biological apatite [32]. Different CS ceramics possess variable apatite-forming ability during immersion in SBF [118]. Apatite formation in CS ceramics is directly associated with their chemical composition and dissolution. For instance, hardystonite possesses no obvious apatite formation and its dissolution is quite slow. In contrast, akermanite exhibits good apatite formation. This apatite layer possesses a distinct morphology with regard to different chemical composition morphology [20]. The incorporation of metal ions such as Zn, Sr, Mg, and Zr into CS ceramics decreases their apatite formation. In addition, it has been revealed that dissolution can have an important effect on the apatite-forming ability of CS ceramics [118]. All the issues mentioned above indicate that metal ions play an important role in the chemical stability and apatite formation of CS ceramics.

IV. Different Forms of Ion-Doped CS ceramics

(1) Calcium magnesium silicate (CaO-MgO-SiO_2)

(a) *Bredigite*

Bredigite is a CS ceramic with the formulation $Ca_7MgSi_4O_{16}$. The crystalline structure of bredigite is orthorhombic and often not pure and there are other minerals associating with it [119, 120]. Ionic dissolution products from this bioceramic promotes cell growth at 6.25 to 50 mg/ml but decreased at 100 and 200 mg/ml and other studies showed that when the concentration of Ca, Si and Mg ions increased to 0.28, 9.95 and 0.24 mM respectively osteoblast proliferation decreased [13, 120]. Bredigite is a cytocompatible CS ceramic [121]. Wu *et al.* reported that bredigite scaffolds with the biomimetic apatite layer and stimulate osteoblasts-like cells (HOB) proliferation to a greater extent than β-TCP [121]. Wu *et al.* showed that ionic dissolution products from diopside, akermanite and bredigite ceramics stimulate OB proliferation at the concentration between 1.25 and 12.5 mg/ml, whereas on increase in the concentration, osteoblast proliferation is decreased. Furthermore, when the concentration reaches 100 mg/ml, no stimulatory effect is observed [122]. Wu *et al.* revealed that bredigite induced HA formation on the surface and promoted OB cell growth [13]. Hui *et al.* reported that bredigite can induce apatite formation [123]. Hu *et al.* reported on the antibacterial activity of bredigite with an increase in the aqueous pH value [124]. Zhai *et al.* indicated that bredigite stimulated human bone marrow mesenchymal stem cell (hBMSC) proliferation and human aortic endothelial cell (HAEC) angiogenesis to a greater extent than diopside [125]. Zhou *et al.* reported that bredigite extracts in concentrations of 12.5 to 100 mg/ml considerably increased periodontal ligament cell (PDLC) proliferation and showed a strong procementogenic effect. However, at 200 mg/ml, cell proliferation significantly decreased [126]. Razavi *et al.* reported that the bioactivity of magnesium alloy is enhanced by bredigite coating [127].

(b) *Diopside*

Diopside ($CaMgSi_2O_6$) is another CS ceramic that has *in vitro* apatite formation ability and can bond to bone tissue [128, 129]. Diopside has a very low degradation rate and can bond directly with bone tissue [99]. Diopside has a monoclinic structure [122]. Generally, diopside has shown no sign of toxicity and can form a uniform junction with the new bone tissue [99, 130, 131]. The combination of diopside with fluroapatite, wollastonite and akermanite can increase bioactivity [132]. Diopside has desirable biocompatibility [49, 99, 106]. Iwata *et al.* concluded that an apatite layer is formed on the surface of diopside during immersion in SBF owing to the dissolution of Ca ions [49, 133]. Masanobu *et al.* stated that TCP-diopside composite forms an apatite layer on the surface [103]. Previous studies reported that

large-size diopside microspheres provided sufficient surface area for bone OB attachment [134]. Wu *et al.* showed that porous diopside microsphere has apatite forming capability in SBF and controlled drug release [135]. Diopside has a similar structure to akermanite and CS but it has a lower degradation rate and proliferated OB more obviously than akermanite and bredigite. Also, with an increase in the Mg content, apatite formation decreased [122]. Wu *et al.* reported that diopside scaffolds exhibit stability and a near-low degradation rate and the scaffolds support HOB proliferation [136]. Diopside is suitable for bonding between substrate and coating [137, 138]. Xue *et al.* reported that diopside coating shows an apatite layer on the surface of titanium alloy [138]. Sainz *et al.* reported that wollastonite-diopside possesses high reactivity in SBF and the dissolution rate can be controlled [139]. Zhang *et al.* stated that HA-diopside exhibits good biological activity [140]. Zhang *et al.* reported that alumina-diopside composite has good biological reactivity [141]. Liu *et al.* revealed that diopside shows bacteria suppression and favourable osteogenic differentiation [142]. Zhang *et al.* showed that diopside scaffolds considerably increase *in vitro* osteogenic differentiation of PDLC compared to β-TCP [143]. Zhai *et al.* reported that diopside stimulates osteogenic differentiation of PDLC and angiogenesis of HAEC [125]. Liu *et al.* stated that diopside scaffolds support proliferation and differentiation of PDLC compared to β-TCP [144]. Luo *et al.* revealed that diopside sphere shows comparable *in vivo* osteogenesis with that of β-TCP [145].

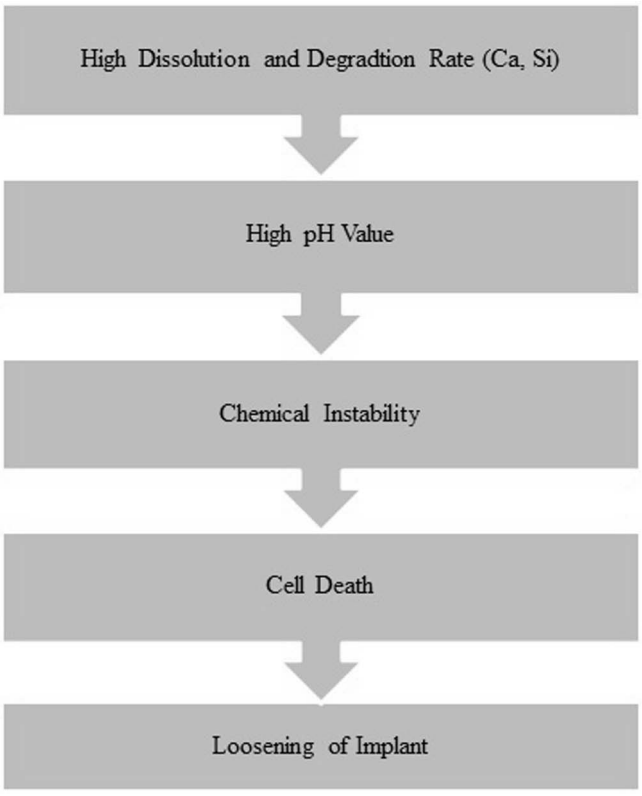

Fig. 4: The high dissolution and degradation rate of CS ceramics and elevated environmental pH indicating their chemical instability.

(c) ***Merwinite***

Merwinite is another CS ceramic with the formulation $Ca_3MgSi_2O_8$ [109]. Hafezi *et al.* showed that an apatite layer is formed on the surface of the merwinite [146]. This material has a monoclinic structure [146, 147]. Hafezi *et al.* reported that merwinite stimulates HA on the surface [147]. Ou *et al.* concluded that an apatite layer can be formed on the surface of merwinite [24]. Abbasi *et al.* showed β-TCP- merwinite nano-composites provoke the formation of an apatite layer [148]. Hafezi *et al.* reported faster new bone formation compared to HA and untreated defect *in vivo* and a faster degradation rate than HA [149]. Chen *et al.* stated that ionic dissolution products from the merwinite significantly enhance OB cell proliferation and, with an increase in the Mg content, the apatite formation ability and cell proliferation decrease.

(d) ***Akermanite***

One of the other CS ceramics is akermanite ($Ca_2MgSi_2O_7$). Akermanite is degradable and has apatite formation ability as well as a tetragonal structure [23, 50, 147]. Wu *et al.* reported that a HA layer can be formed on the surface of akermanite [25]. Liu *et al.* concluded that akermanite has better cell proliferation of human adipose-derived stem cells (hASC) than β-TCP [2]. Xia *et al.* demonstrated that akermanite enhance the proliferation of periodontal cells compared to β-TCP [3]. Sun *et al.* showed that akermanite increases cell proliferation and improves the differentiation of bone-marrow-derived stromal cells (BMCs) [150]. Bhatkar *et al.* stated that akermanite has good potential for use as a biomarker in controlled drug delivery [151]. Hou *et al.* concluded that the surface morphology plays an essential role in the *in vitro* behaviour and bioactivity of akermanite ceramics [152]. Huang *et al.* reported that in a 1.256 dilution of 200 mg/ml concentration, *in vitro* proliferation and differentiation of BMCs are increased compared to β-TCP and shows a faster degradation and higher bone formation rate *in vivo* in a rabbit model than β-TCP does [153]. Wu *et al.* reported that akermanite has better bone-like apatite formation ability compared to bioactive wollastonite and that a HA layer is formed on the surface and enhances OB proliferation [154]. Gu *et al.* revealed that ionic products from akermanite could assist the proliferation of hASCs and osteogenic differentiation when the concentration of Ca, Si and Mg ions reaches around 2.36, 1.11 and 1.03 mM respectively [155]. Wu *et al.* revealed that porous akermanite scaffolds form HA on the surface and also BMCs adhere properly to the scaffolds [50]. Zhai *et al.* reported that akermanite shows better neovascularization compared to β-TCP [156]. Wu *et al.* showed that HA formation takes place on the surface of akermanite [157]. Liu *et al.* stated that the PLGA-akermanite composite enhances the biological and physicochemical properties to a greater extent than pure PLGA [144]. Goudouri *et al.* revealed that in akermanite scaffolds an apatite layer is formed on the surface after immersion in SBF [158]. Razavi *et al.* reported that an akermanite coating improves the corrosion resistance and *in vitro* bioactivity of magnesium alloys [159]. Hu *et al.* stated that the anti-bacterial

effect of akermanite is dose-dependent, the Ca content playing an important role in the anti-bacterial activity [124]. Zhai *et al.* showed that akermanite stimulates cell proliferation of hBMSC and angiogenesis of HAEC to a greater extent than diopside [125]. Chen *et al.* reported that akermanite can considerably stimulate cell proliferation at concentrations between 1.25 and 125 mg/ml and cell proliferation is obvious in 12.5 mg/ml while when the concentration reaches 100 mg/ml no obvious stimulatory effect is observed [160]. Wu *et al.* showed that akermanite enhances OB proliferation and has intermediate ion degradation compared to bredigite and diopside. Yi *et al.* reported that an akermanite coating on Ti alloy shows a distinct apatite layer after immersion in SBF and the proliferation of rBMSC cells is higher than that of HA [161]. With an increase in the MgO content, Mg atoms inhabit Ca atoms in the structure and make the structure more stable [162].

(da) ***Strontium-doped akermanite (Sr-CaO-MgO-SiO_2)***

Zhang *et al.* stated that Sr-modified akermanite ceramic enhances the growth of bone marrow mesenchymal stem cells (BMSC) compared to β-TCP [163].

(e) ***Monticellite***

One other CS ceramic is monticellite with the formulation $CaMgSiO_4$. Monticellite has a trimetric structure [162]. Chen *et al.* revealed that monticellite exhibits apatite formation ability on soaking in SBF and enhanced OB proliferation [164]. Chen *et al.* showed that monticellite considerably enhances OB and, on increase in the MgO content, the apatite formation ability decreases [162]. Monticellite bioceramic exhibits a biological performance comparable with that of akermanite and bredigite [109, 164].

(2) Calcium Zirconium Silicate ($CaO-ZrO-SiO_2$)

(a) ***Baghdadite***

Another CS ceramic is baghdadite with the formulation $Ca_3ZrSi_2O_9$ [31, 165]. Baghdadite is cytocompatible and has a monoclinic structure [7, 166]. Roohani-Esfahani *et al.* reported that baghdadite can sustain bridging in large bone defects [31]. Liang *et al.* revealed that a baghdadite coating improves chemical stability and tight bonding with the surface and shows the formation of an apatite layer on the substrate [165]. Ramaswamy *et al.* stated that baghdadite sustains adhesion, growth and differentiation of osteoclasts (OCs) and OB without any toxic effect [7]. Luo *et al.* stated that baghdadite spheres significantly enhance *in vivo* osteogenesis compared to diopside and β-TCP [145].

(3) Calcium titanium silicate ($CaO-TiO-SiO_2$)

(a) ***Sphene***

One other CS ceramic is sphene (SP) with the formulation $CaTiSiO_5$ [34,167–170]. Wu *et al.* showed that SP possesses a monoclinic structure, improves chemical stability and supports human bone-derived cells (HBDC) proliferation compared to CS and TCP [34]. Ramaswamy *et al.* revealed that SP ceramics enhance osseointegration and bone formation around the implant without fibrous tissue response and shows maximum HOB cell proliferation at 100 – 200 mg/ml [167]. Wu *et al.* reported that SP coatings significantly enhance chemical stability compared to HA coatings and SP coatings possess apatite-formation ability in SBF [169]. Wu *et al*. reported that SP coatings possess considerably improved chemical stability and enhance human HOB proliferation compared to HA and unmodified Ti substrate [170]. Wang *et al.* reported that SP enhances HOB proliferation and attachment [168].

(4) Calcium zinc silicate ($CaO-ZnO-SiO_2$)

(a) ***Hardystonite***

One other CS ceramic is hardystonite with the formulation $Ca_2ZnSi_2O_7$. This ceramic has a tetragonal structure in which Zn reacts with Ca, Si and O and forms a new crystal phase of hardystonite according to the following reaction:

$$(x)Zn+Ca+Si+(3+x)O \rightarrow (x)Ca_2ZnSi_2O_7+(1-2x)CaSiO_3 \quad (1)$$

Hardystonite is more chemically stable compared to CS ceramics and the presence of Zn ions affects the roughness of the ceramic. In addition, 0.4 ppm Zn ions (50 % Zn concentration) possesses the best chemical stability, contributes to HOB cell proliferation and differentiation and inhibits apatite formation [33]. It was reported that hardystonite is not naturally pure owing to the presence of other minerals such as willemite (Zn_2SiO_4) as shown by the chemical synthesis of hardystonite. The willemite structure accommodates the Zn atoms in two different 4-fold coordination sites, thus forming a new crystal phase via a reaction with Ca, Si and oxygen [171,172]. Courthéoux *et al.* showed that Zn makes the CS glass network intricate, slows dissolution of the glass and enhances its chemical stability (durability) [173]. Wu *et al.* showed that bone marrow mesenchymal stem cells (BMMSC) adhere well to the surface of the hardystonite [174]. Zreiqat *et al.* reported that *in vivo* hardystonite implantation in tibial bone defects of rats shows rapid new bone growth compared to β-TCP [32]. Wang *et al.* revealed that the hardystonite-CS scaffold has a lower degradation rate compared to CS ceramics and hardystonite-CS scaffolds show better HOB attachment than CS scaffolds [4]. Ramaswamy *et al.* showed that hardystonite shows maximum HOB proliferation in the extract concentration of 6.25 to 200 mg/ml with no toxic effect compared to CS [27]. Li *et al.* reported that with a hardystonite coating on Ti-6Al-4V alloy, chemical stability improves considerably and absorbance of extract concentrations from 0.125 to 1 cm^2/ml shows no cytotoxicity effect and mouse calvaria-derived osteoblasts-like cells (MC3T3-E1) proliferate with decreasing extract concentrations [175]. Li *et al.* demonstrated the *in vitro* cytocompatibility of a hardystonite coating and revealed that the hardystonite kills the bacteria through initial structural and morphological damage to the cell membrane owing to the presence of Zn ions [176]. Jiangming *et al.* revealed that a hardystonite coating shows improved MC3T3-E1 cell differentiation, attachment and proliferation and *in vivo* rabbit femur defect studies showed faster osseoin-

tegration compared to CS [177]. Wang *et al.* reported that a hardystonite coating shows a higher proliferation rate of HOB than an SP coating owing to the presence of Zn ions [168]. Xiong *et al.* reported that a Zn-containing porous layer slows down the dissolution rate, has no influence on OB cell adhesion, an apatite layer formes on the surface and MC3T3-E1 adheres well to the surface [115]. Liu *et al.* showed that at the concentration of 12.5 mg/ml hardystonite, the PDLC number was higher than for β-TCP. However, at the concentrations of 50 and 200 mg/ml, the cell number of β-TCP is higher than HT and at the 6.25 mg/ml HT shows significantly higher PDLC [142].

(aa) ***Strontium-doped hardystonite (Sr-CaO-ZnO-SiO_2)***

Zhang *et al.* stated that Sr-doped hardystonite or $Sr_2ZnSi_2O_7$ possesses a tetragonal crystal structure the same as hardystonite, and both exhibit a low degradation or dissolution rate. The reason for the relatively low dissolution (excellent chemical stability) of $Sr_2ZnSi_2O_7$ in comparison to Sr-$CaSiO_3$ is its intrinsic crystal structure. Rabbit bone-marrow stem cells (rBMCs) adhere well to the surface owing to its materials chemistry (Sr and Zn ions), confirming its *in vitro* biocompatibility [37]. Boyd *et al.* showed that Sr-doped hardystonite glass ceramic with 0.28 mol fraction SrO increases loading and may facilitate charge compensation of Zn^{2+} in the network to form stable Zn/Sr tetrahedron, which is replaced with SiO_2, increasing the network stability, and shows a mild to moderate cytotoxic effect in a standard femur model. However, 0.12 mol fraction SrO does not considerably affect the structure [178]. Lu *et al.* demonstrated that in non-contact mode (tissue culture plate), both hardystonite and β-TCP support BMC cell proliferation and osteogenic differentiation, but hardystonite has a much greater effect than β-TCP, which is attributed to the ions, such as Ca, Si and Zn, dissolved from the hardystonite ceramic. However, in contact mode (ceramic disks) the β-TCP promotes cell proliferation whereas hardystonite does not [179]. Roohani-Esfahani *et al.* showed that HOB is spread on the surface of Sr-hardystonite-gahnite scaffolds and considerably increases osteogenic gene expression in a rabbit radius with no toxic or inflammatory effects [180]. Zhang *et al.* reported that Sr-hardystonite coatings show fast *in vivo* bone formation and *in vitro* functionality of BMMSC mainly due to the Sr ionic dissolution [181]. Jaiswal *et al.* revealed that hardystonite-polycaprolactone (PCL) scaffolds enhance murine adipose-tissue-derived stem cells (mE-ASC) proliferation, cellular infiltration and improve mineralization of matrix compared to HA-PCL scaffolds. This increase in cell proliferation can probably be attributed to the presence of Zn and Si ions in the hardystonite structure [182]. Zhang *et al.* revealed that the extracts of Sr-doped hardystonite in a wide concentration range support the growth of bone marrow mesenchymal stem cells (BMSC) compared to β-TCP, indicating no obvious cytotoxicity [163]. Li *et al.* reported that according to Equation 1, with 0.3 and 0.5 mol Zn, mixed phases of hardystonite and Ca-SiO_3 and only hardystonite are found, respectively. The hardystonite coating shows improved chemical stability and antibacterial properties with an increase in the Zn content and reveals significantly enhanced MC3T3 cell proliferation compared to the uncoated Ti and $CaSiO_3$ coating and optimal content is 0.5 mol Zn [183]. However, the coating containing 1.0 mol Ca/Zn, in which both hardystonite and ZnO are found, obviously induces cell death owing to much higher amounts of Zn^{2+} ions. A previous report showed that a Zn^{2+} ion concentration of 10 ppm could induce 50 % cell death [184]. The mechanism of improved chemical stability is as follows: with Zn incorporation, a more stable and less soluble hardystonite crystal structure is formed. Hardystonite belongs to the sorosilicate structures, in which two silicate tetrahedrons are connected by one oxygen ion and therefore the basic chemical unit is $[Si_2O_7]$ [185, 186] In the crystal structure of hardystonite, the Zn^{2+} ions are in a four coordination, and the ZnO_4 tetrahedron and Si_2O_7 group form a more stable network that prevents release of Ca and Si ions. It was thought that released Zn^{2+} ions react with the cellular membrane and disrupt its function, which leads to cell death [187]. Roohani-Esfahani *et al.* reported that the extract of Sr-doped hardystonite and aluminium oxide (Al_2O_3) scaffold shows no cytotoxicity effect on HOB proliferation at 200 mg/ml [188]. Zreiqat *et al.* reported that compared to HT scaffolds, Sr-HT ceramic scaffolds induce the attachment and differentiation of human-bone-derived cells (HOB) [32].

V. Conclusions

It is obvious that metal ions can play an important role in numerous processes related to bone formation. It is also observed that the delivery of metal ions motivates new bone formation. However, the high dosages of metal ions in the environment are questionable owing to the toxic effects and it must be guaranteed that the dosages of the metal ions lie within a window of efficiency. In addition, interactive effects of more than one ion may overlap, which is a phenomenon that has not been fully understood. There is therefore notable scope for further research to explain the role of metal ions in bone-associated physiological processes at a more fundamental level.

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