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Ion-Doped Silicate Bioceramic Coating of Ti-Based Implant

Hossein Mohammadi[1] and Mohammadmajid Sepantafar[2,3*]

[1]School of Materials and Mineral Resources Engineering, Universiti Sains Malaysia, Engineering Campus, 14300 Nibong Tebal, Penang, Malaysia; [2]Department of Stem Cell and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran; [3]Department of Metallurgy and Materials Engineering, Faculty of Engineering, University of Semnan, Semnan, Iran

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ABSTRACT

Titanium and its alloy are known as important load-bearing biomaterials. The major drawbacks of these metals are fibrous formation and low corrosion rate after implantation. The surface modification of biomedical implants through various methods such as plasma spray improves their osseointegration and clinical lifetime. Different materials have been already used as coatings on biomedical implant, including calcium phosphates and bioglass. However, these materials have been reported to have limited clinical success. The excellent bioactivity of calcium silicate (Ca-Si) has been also regarded as coating material. However, their high degradation rate and low mechanical strength limit their further coating application. Trace element modification of (Ca-Si) bioceramics is a promising method, which improves their mechanical strength and chemical stability. In this review, the potential of trace element-modified silicate coatings on better bone formation of titanium implant is investigated.
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Keywords: Plasma spray, Modified silicate ceramics, Coating, Ti implant

Corresponding Author: Mohammadmajid Sepantafar
Department of Stem Cells and Developmental Biology at Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, P.O. Box 19395-4644, Tehran, Iran. Tel: (+98-21) 22306485; Fax: (+98-21) 66959104; E-mail: Sepantafar@gmail.com

INTRODUCTION

One of the most successful economical and surgical procedures for bone tissue repair is total joint replacement. This procedure could enhance function and movement and decrease pain in patients suffering from severe arthritis and skeletal tissue abnormalities[1].

The successful performance of biomedical implant mainly relies on the suitable osseointegration at the interface of host tissue and biomaterial[2]. Osseointegration is occurred when functional integrity is created directly between the bone tissue and the surface under load implant[3].

Ti-6Al-4V is a well-recognized biomaterial with proper mechanical features and biocompatibility, which are found in many biomedical implants such as bone screw. However, the lack of biodegradability, the slow rates of osseointegration and poor mechanical anchorage result in implant failure and loosening[4-9]. Furthermore, a fibrous layer is formed at the interface between the implant and tissue. Also, local inflammation and infection are occurred most probably due to the long-term presence of implant *in vivo*[10].

The available synthetic implants still have restrictions in clinical practice and need revision surgery due to the formation of thick fibrous tissue at the tissue-biomaterial interface[11,12]. The revision surgery decreases the quality of the life of people suffering from hard tissue diseases, since it is more difficult than the initial surgery. Many attempts have been performed on the quality of available biomedical implants by surface modification. As stated above, development of new implants coated with bioactive and functionally stable materials is necessary. Different surface modification methods have been employed to modify the surface of currently available biomedical metallic implants[13]. The coating materials play an

important role in providing an environment in which bone formation ability is enhanced and in turn, better integration is established between the implant and bone tissue. Various surface modification methods have been used to encourage the bone formation between tissue and medical implant[14-16], including chemical vapor deposition[17,18], anodic oxidation[19], sol-gel[6,20], physical vapor deposition[6,21], plasma spray[22], electrophoretic deposition (EPD)[23], anodic spark deposition[2] and enameling[24,25].

Bioceramics, such as calcium phosphate[26], hydroxyapatite (HA)[27,28] and calcium silicate (Ca-Si)[29] have been used as coating materials on the surface of biomedical implants. HA could directly bond with the bone tissue with no fibrous layer formation[27,28]. However, it possesses low osteogenic activity[30,31], inadequate chemical stability[32,33], mismatch of thermal expansion coefficient (CTE) with Ti-6Al-4V substrate[34,35] and low bonding strength[36,37], which lead to short-term osseointegration. The mismatch of CTE between HA coating and Ti substrate provides higher tensile strength at the interface, decreases the bonding strength of coating and may cause peeling and fatigue failure under tensile loading[38]. Also, bioglasses[39,40] have been applied to modify the surface of medical implants. However, most of the bioglasses coatings have poor bonding strength due to the mismatch of their CTE with Ti-6Al-4V[41] and high degradation rate[42].

Ca-Si-based ceramics have shown to have higher bonding strength with Ti substrate compared to HA[29]. Further, they could support osteoblast attachment as well as proliferation and differentiation by the release of calcium (Ca^{2+}) and silicon (Si^{2+}) ions[43-45]. Also, the dose-dependent antibacterial activity of Ca-Si-based ceramics has been also demonstrated in some studies[46,47]. Silicate bioceramics possess comparable CTE with Ti-6Al-4V; as a result, the high bonding strength is provided and also the residual stress is decreased[35,48,49]. However, their chemical instability, inability to support human bone formation and poor mechanical properties limit their applications as a biomedical coating for long-term orthopedic implants[50].

It has been reported that the positive ion modification (trace element) improves the biological and mechanical strength of Ca-Si-based ceramics[51,52], which may increase their bone bonding ability[53,54]. Therefore, it is reasonable to use trace element-incorporated silicate bioceramic as coating materials for metallic implants. The objective of this review is to investigate whether the ion-modified Ca-Si coating can effectively improve the osseointegration of implant and, in turn, the quality of life of patients compared to conventional ceramic coatings.

Various characteristics of ideal biomedical coating

Structural properties

A coating material with ideal biocompatibility and bioactivity is considered as a perfect material for orthopedic applications because the direct contact between the underlying implant and bone tissue is inhibited and in turn, the release of challenging ions from the implant is decreased[55]. Further, high bonding strength may be provided with underlying substrate. The chemical stability and the low degradation rate in biological environment influences their long-term durability[6,34]. Also, the coating material with nanostructural configurations is favorable for the absorption of ions such as Ca^{2+} and magnesium (Mg^{2+})[56-59], which result in better osteoconductivity[60]. The other features that may influence the establishment of good bonding strength between the underlying implant and coating *in vitro* and *in vivo* include surface roughness, thickness, microstructures[6,35,61], Young's modulus and CTE[62,63]. Rough surface is favorable for cell attachment and proliferation, which are valuable for bone implant fixation[64]. However, the presence of microcracks in the surface is not advantageous for corrosion resistance and the good bonding strength[65].

Cell-coating interaction

Biological reactions are generally occurred on the surface; therefore, the surface characteristics of coating such as ion release and topography are key factors in the implant-cell interactions[66-68] (Fig. 1).

As indicated in Figure 2, the surface properties of the implant are improved by coating, and apatite formation is induced on the surface leading to a better bonding

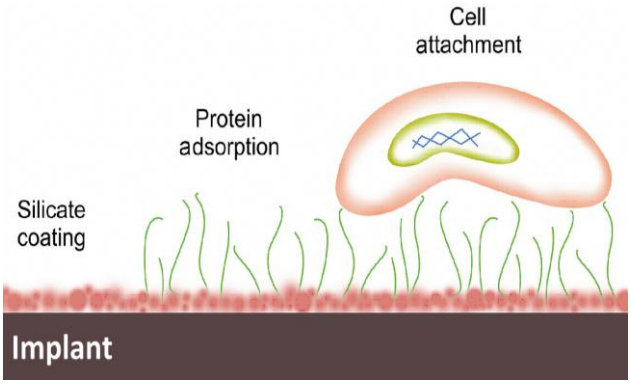

Fig. 1. The effect of released ions on osseointegration and antibacterial properties.

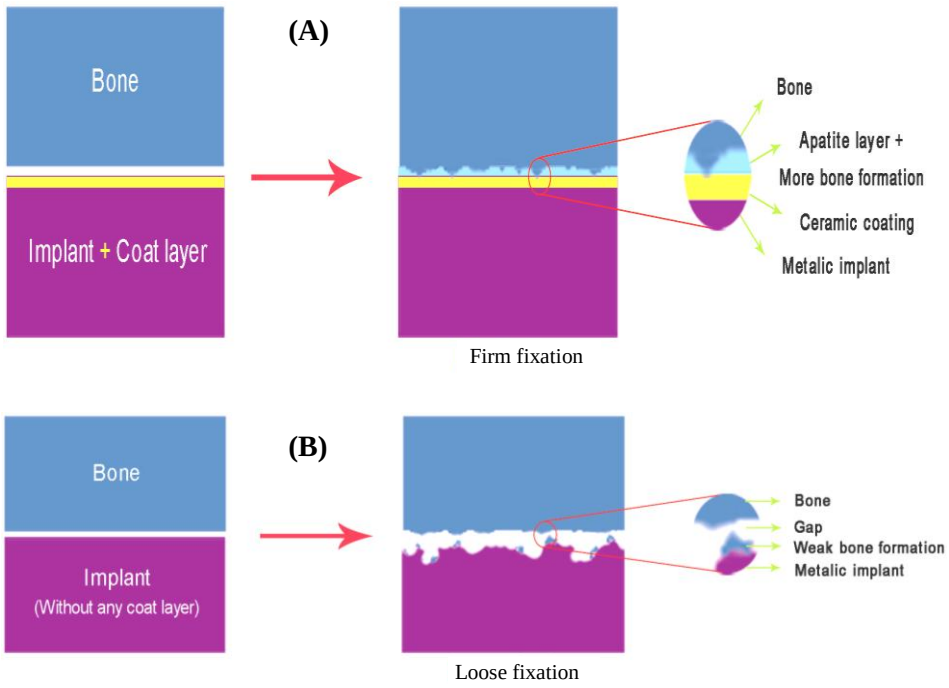

Fig. 2. The effect of ceramic coating on the Ti substrate. (A) The implant without coating leads to weak bone formation and the loosening of the implant; (B) the apatite formation on the implant with coating resulted in more bone formation and tight fixation of implant.

with bone tissue (Fig. 2A) compared to uncoated substrate (Fig. 2B). The formation of a silica layer on the surface is beneficial to the adsorption of proteins. This silica layer supports and facilitates the interactions between proteins and the surface of material and, in turn, affects cell behaviors[69]. Hence, the cell-material interaction may be effective in establishing a tight bonding with the host bone tissue, which provides a suitable substrate for cell attachment. Also, it is notable that the cell proliferation rate is related to initial cell attachment density[63].

The surface chemistry may affect the adsorption of proteins from the surrounding medium to facilitate the cell attachment[70]. Also, more binding sites can be provided for the adsorption of protein by Si^{4+} ions[71]. Briefly, the molecular mechanism by which the interaction is established between the cells and underlying substrate may be described as follows.

After *in vitro* and/or *in vivo* implantation, several biological reactions occur on the surface of implant. First, proteins are immediately adsorbed to the surface of implant[72]. Next, integrins may be bound to proteins, which transduce extracellular signals inside the cells[68,69]. As a result of these signaling pathway, the cell behavior can be altered through the regulation of those genes whose functions are associated with attachment, proliferation and differentiation. Herein, the characteristics of the surface may determine the orientation of adsorbed proteins and the expression of integrins[70].

When the coated implant is placed *in vivo*, the coating materials are exposed to physicochemical and/or cell-mediated dissolution and corrosion. As a result, it can be degraded and replaced by newly formed bone tissue[73]. Therefore, it is suggested that the release of ions from the bioceramic coating controls the local microenvironment, which determines the host cell behavior and supports the new bone formation process. It is thought that the chemistry and the microstructure of the surface are responsible for advantageous stimulatory effect.

Trace element-modified calcium silicate ceramic coating

The $CaSiO_3$ and Ca_2SiO_4 coatings have shown to have excellent *in vitro* bioactivity. In addition, these types of coatings demonstrate a rough microstructure and higher bonding strength compared to HA[6,29,32,33]. Nonetheless, both HA and $CaSiO_3$ coatings possess rapid degradation rate, which resulted in disintegration of the coatings and compromising their bonding strength and implant fixation[74]. Although there are no microcracks between the Ca_2SiO_4 coating and the substrate[29], the short-term osseo-integration[29,75,76] and poor chemical stability[49] are major problems that hinder the *in vivo* long-term durability of implants.

It is known that the incorporation of ions into CaO-SiO_2 improves the chemical stability and mechanical properties compared to HA and $CaSiO_3$. In addition, ion-modified CaO-SiO_2 materials have apatite-forming ability in simulated body fluids[51,52].

The feedstock (CaO-ZrO_2-SiO_2 [CZS]) is one of the Zr-modified materials. The atmospheric plasma or air plasma (APS)-sprayed CZS on Ti-6Al-4V substrate[77] has exhibited a higher bonding strength than plasma-sprayed HA coating[22]. This higher bonding strength of CZS coating is attributed to the large content of zirconia in the CZS coating. Also, CZS coating has high strength and good toughness due to the comparable CTE of CZS coating and Ti-6Al-4V[78,79]. It has been shown that the *in vitro* cytocompatibility of CZS coating on Ti substrate can promote the adherence of a large number of canine marrow stem cells (MSCs) to the material[77]. Furthermore, the MSCs well proliferate on CZS, which can be due to the rough surface of coating. However, the cell proliferation rate of CZS and HA is similar. A report has demonstrated that bone marrow-derived stromal cells (BMSCs) firmly adhere to the surface of CZS coating and show a considerably faster cell proliferation compared to HA coating[79]. It has been suggested that the presences of Si^{4+} ions positively affect the cell behavior. In addition, silicon-enriched layer formed on the surface of CZS is beneficial to protein adsorption and cell attachment[79].

The second Zr-modified material is Baghdadite ($Ca_3ZrSi_2O_9$). The $Ca_3ZrSi_2O_9$ coating on the Ti-6Al-4V substrate using APS has been shown to have stronger bonding strength with Ti substrate[80] compared to plasma sprayed-HA coating[81]. Although the surface roughness of $Ca_3ZrSi_2O_9$ is higher than CZS, it possesses lower bonding strength.

There are different Mg-modified compounds that show good bonding strength and better biocorrosion and antibacterial properties compared to HA and β-TCP. These compounds include akermanite ($Ca_2MgSi_2O_7$), diopside ($CaMgSi_2O_6$), bredigite ($Ca_7MgSi_4O_{16}$), merwinite ($Ca_3MgSi_2O_8$) and monticellite ($CaMgSiO_4$)[52].

The $Ca_2MgSi_2O_7$-coated Ti-6Al-4V by APS[48] indicated that the bonding strength of the coating is much higher than HA[22,36,82]. However, the mismatch of CTE between $Ca_2MgSi_2O_7$ and underlying Ti substrate leads to the formation of longitudinal cracks inside the coating. Thus, the bonding strength of $Ca_2MgSi_2O_7$ is lower than $CaMgSi_2O_6$ due to the presence of microcracks.

The $CaMgSi_2O_6$-coated Ti-6Al-4V using plasma spray has exhibited higher bonding strength compared to HA[34]. This higher bonding strength is due to the comparable CTE of $CaMgSi_2O_6$ and underlying Ti substrate, which prevents the formation of microcracks at the interface[34].

$Ca_7MgSi_4O_{16}$ can also be applied as a coating material on the implant surface. When $Ca_7MgSi_4O_{16}$ is coated on the Ti-6Al-4V surface[83], the bonding strength is higher than HA[22], wollastonite[84], Ca_2SiO_4[29], $CaMgSi_2O_6$[34], $CaTiSiO_5$[35] and $Ca_2MgSi_2O_7$ coatings[48]. This high bonding strength is mainly due to the tight interface between coating and underlying surface, no clear microcracks and well-melted $Ca_7MgSi_4O_{16}$ powder. The BMSCs adhere well on the surface with a higher proliferation rate than HA. This is ascribed to the capability of bone-like apatite layer enhancing the osteoblastic activity[85-87] and stimulating the role of Mg^{2+} and Si^{4+} ions[88-91]. Although both $Ca_2MgSi_2O_7$ and $Ca_7MgSi_4O_{16}$ showed bonding strength higher than HA, $Ca_2MgSi_2O_7$ had lower bonding strength compared to $Ca_7MgSi_4O_{16}$ due to microcracks (Fig. 3).

$Ca_3MgSi_2O_8$ and $CaMgSiO_4$ are the next materials with a potential use as coating. The CTE of both is closer to that of Ti-6Al-4V alloy[92]. However, no data are available in the literature focusing on their applications as coating on Ti-6Al-4V substrate.

$Ca_2ZnSi_2O_7$ is the other ion-modified material with enhanced mechanical, biological and antibacterial properties. The coating of $Ca_2ZnSi_2O_7$ on Ti-6Al-4V surface through APS obtained the higher bonding strength compared HA coating[93] mainly because of their comparable CTE[94]. The plasma-

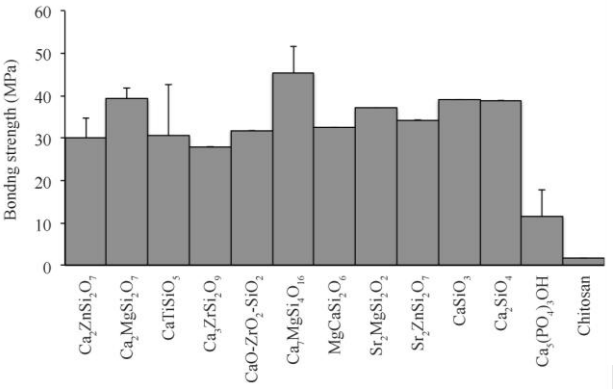

Fig. 3. Bonding strength of coating reported in the literatures for hardystonite ($Ca_2ZnSi_2O_7$)[49,93], akermanite ($Ca_2MgSi_2O_7$)[48], sphene ($CaTiSiO_5$)[20,35,93], baghdadite ($Ca_3ZrSi_2O_9$)[80], CaO-ZrO_2-SiO_2 feedstock (CZS)[77], bredigite ($Ca_7MgSi_4O_{16}$)[83], diopside ($MgSi_2O_6$)[34], $Sr_2MgSi_2O_7$ (SMS)[42], $Sr_2ZnSi_2O_7$ (SZS)[100], $CaSiO_3$[6], Ca_2SiO_4[29], hydroxylapatite ($Ca_5(PO_4)_3OH$)[6,22,29,32-34,36,49,81,82] and chitosan[13,111]. Also, for baghdaditeand akermanite, there was no accurate value for bonding strength; a range of bonding strength value was reported.

sprayed $Ca_2ZnSi_2O_7$ on Ti-6Al-4V surface also showed a significantly higher bonding strength than HA[49]. Further, the coating supported primary human osteoblasts cell and osteoblast-like cell line (MC3T3-E1) attachment, spreading and proliferation[49,55,95] due to the presence of Ca^{2+} and Si^{4+} ions[93]. Moreover, this coating demonstrated a higher bone interface contact and faster osseointegration compared to $CaSiO_3$ without the formation of fibrous tissue. Besides the osteogenic properties, $Ca_2ZnSi_2O_7$ is able to show antibacterial effect against *Escherichia coli* and *Staphylococcus aureus*[49,95]. This antibacterial activity is thought to be related to the initial damage to cell wall and cell membrane.

$CaTiSiO_5$ is a Ti-modified material used as a coating due to the close CTE to Ti-6Al-4V[35,96]. The $CaTiSiO_5$ coating on Ti-6Al-4V demonstrated a bonding strength considerably higher than HA and $Ca_2ZnSi_2O_7$[93]. This superior bonding strength of the $CaTiSiO_5$ compared to $Ca_2ZnSi_2O_7$ is probably due to the presence of Ti^{4+} in the $CaTiSiO_5$, which may improve the chemical and diffusion bonding between $CaTiSiO_5$ and the underlying Ti-6Al-4V substrate[97]. However, the $Ca_2ZnSi_2O_7$ showed a rougher surface compared to $CaTiSiO_5$. It should be noted that $CaTiSiO_5$ coating on Ti-6Al-4V can be prepared by sol-gel spinning[20]. The prepared $CaTiSiO_5$ showed a higher bonding strength than HA but lower than plasma-sprayed $CaTiSiO_5$. The higher bonding strength is thought to be related to the inherent properties of $CaTiSiO_5$. However, both soaking the Ti-6Al-4V implant in $CaTiSiO_5$ sol-gel solution and HA showed high bone-implant contact, while uncoated Ti-6Al-4V revealed a significant poor bone-implant contact due to the presence of wide fibrous tissues. Moreover, both HA and $CaTiSiO_5$ coatings exhibited comparable mechanical fixation but $CaTiSiO_5$ showed considerably higher mechanical fixation compared to the uncoated Ti-6Al-4V[96]. Nonetheless, $CaTiSiO_5$ coating indicated higher bonding strength compared to sol-gel spinning but lower strength than plasma-sprayed coating.

The $CaTiSiO_5$ coating on Ti-6Al-4V through plasma spray shows no microcracks at the interface and reveals a strong bonding strength[35] higher than HA[22,33,81,98]. Additionally, the $CaTiSiO_5$ coating could support human osteoblast-like cell attachment, spreading and proliferation, which is due to the presence of Ca^{2+} and Si^{4+} ions. The $Ca_2ZnSi_2O_7$ coating, however, demonstrates a higher proliferation rate than $CaTiSiO_5$ and Ti-6Al-4V substrate, which is related to the release of Zn^{2+} ions from the $Ca_2ZnSi_2O_7$[93].

Evidence has shown that different methods can be used for preparation of $CaTiSiO_5$ coating. Each of the preparation methods has its own advantages and disadvantages. According to the previous reports, the plasma spray technique produces a much denser microstructure compared to the sol-gel method. Nonetheless, using sol-gel method, the coating could be sintered in low temperatures since at higher temperature, it will oxidize and damage the surface of underlying substrate. In addition, the problem of low temperature sintering is that a completely dense microstructure cannot be obtained as observed for sol-gel method, thus affecting the bonding strength[35]. However, the advantages of the plasma spray method as a frequently commercial method for the preparation of coating is high deposition rate and rough surface, which is favorable for bone substitute[6,21].

It is worth noting that the simultaneous incorporation of ions into Ca-Si system is also possible to further improve biological and mechanical integrity. Recently, Sr^{2+} and Ti^{4+} have incorporated into Ca-Si and improved the bioactivity and the proliferation of mesenchymal stem cell compared to $Ca_2ZnSi_2O_7$[99]. This nanocomposite may have the potential to be used as a coating. An investigation has indicated that when Sr^{2+} and Zn^{2+} are incorporated into Ca-Si structure, $Sr_2ZnSi_2O_7$ (SZS) is formed. The SZS considerably controlled the inflammation, decreased the osteoclastogenesis and improved osteogenesis with higher bonding strength compared to HA[100]. The reason is that both Sr^{2+} and Zn^{2+} are found in the structure of natural bone tissue and have stimulatory effect on bone formation. In addition, there were no microcracks at the interface mainly due to the similarity of CTE. Moreover, the presence of Zn^{2+} may induce anti-inflammatory effects after implantation.

Other study has reported that the incorporation of Sr^{2+} and Mg^{2+} into Ca-Si system results in the formation of $Sr_2MgSi_2O_7$ (SMS). This modified coating represented higher capacity to prevent osteoclastogenesis with stronger bonding strength compared to HA. This property is due to the similarity of CTE of coating and substrate as well as the absence of microcracks on the surface of coating[42]. Also, this coating has higher bonding strength than SZS (Fig. 3).

As an example of the *in vitro* bioactivity of these modified ceramic coatings, after soaking SMS in simulated body fluids solution, a lath-like apatite is formed on the surface (Fig. 4). Unlike HA coating, the SMS coating is able to prevent inflammatory

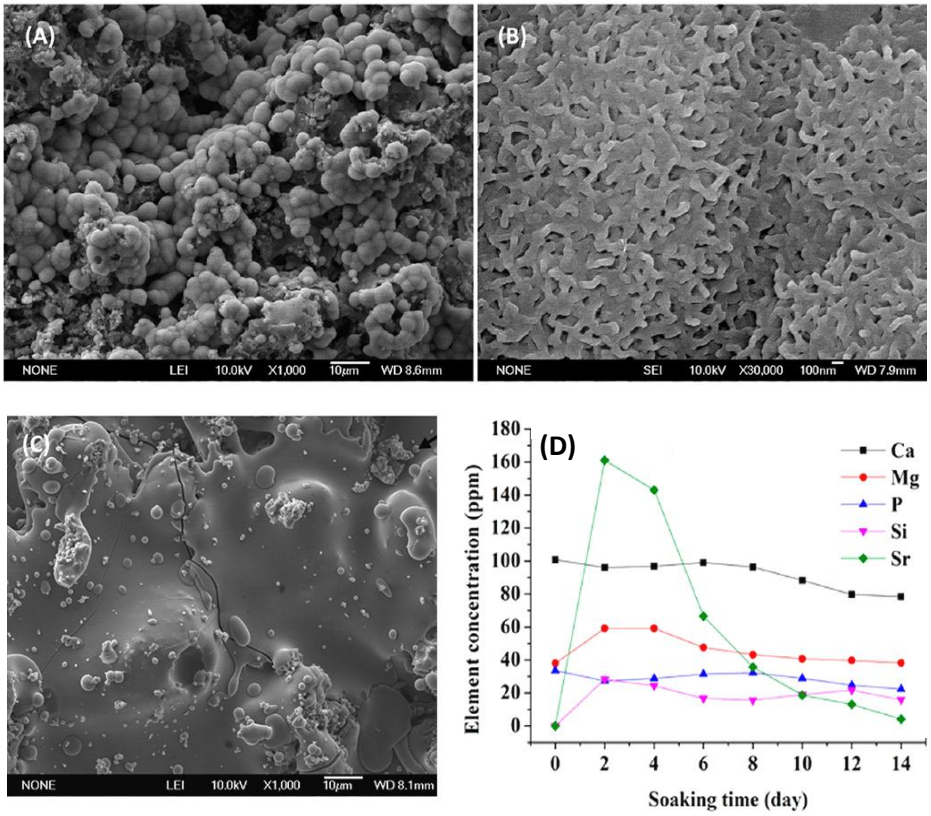

Fig. 4. Scanning electron microscopy images of (A) the apatite layer formed on the surface of SMS coating after immersion in simulated body fluids, (B) lath-like morphology of apatite layer and (C) Ti alloy without coating, indicating that the SMS coating improves the bioactivity if Ti alloy. (D) Release of Sr^{2+} from SMS coating, which is considerably higher than that observed for HA coating, showing possible mechanism for reduced osteoclastogenesis of SMS coating. Reproduced with permission[42], Copyright 2014, ACS applied materials & interfaces.

reaction. The mechanism by which SMS coating inhibits the inflammatory response is that a significant decrease in Ca^{2+} and an increase in Mg^{2+} and Sr^{2+} concentration are occurred, and the formation of fibrous capsule is inhibited by Wnt/Ca^{2+} pathway after implantation[101]. Also, Mg^{2+} and Sr^{2+} can decrease inflammatory cytokine production[102,103]. Mg^{2+} is known to suppress inflammatory cytokine production via the inhibition of toll-like receptors pathway[104] (Fig. 5). However, the mechanism for inhibitory effect of Sr^{2+} is not fully understood. It may be speculated that the possible mechanism for reduced osteoclastogenesis of SMS coating is due to released Sr^{2+} from the coating (Fig. 4)[105]. However, the osteogenic differentiation of BMSCs on SMS is similar to HA. This fact reveals the similar *in vitro* osteogenic-inducing capability of SMS and HA.

EPD accompanied with micro arc oxidation (MAO) is another known method for coating of modified Ca-Si ceramic coating on the metallic substrate[106]. The advantages of the EPD method include the possibility of using versatile materials, cost-effectiveness, application of simple equipment, storage at room temperature, coating in a short time and less restriction applied to substrate shape[107]. In particular, the EPD method is able to produce uniform coating on the substrate compared to other coating techniques. In addition, it has been found that MAO layer is porous with high adhesion strength[108]. Furthermore, MAO is recognized as an effective approach to control the corrosion rate of biodegradable Mg alloy. Therefore, both corrosion resistance and bioactivity of substrate could be enhanced[109,110]. Best of our knowledge, this method has not been used for preparation of modified Ca-Si ceramic coating on Ti substrate. Thus, the preparation of modified Ca-Si ceramic on the Ti substrate using EPD could be the topic of studies in the future. Moreover, the biological response at the tissue-implant interface of surface-modified metallic implants and their *in vivo* mechanism must be carefully identified for new applications and enhance the functionalities of the future generations of medical implants.

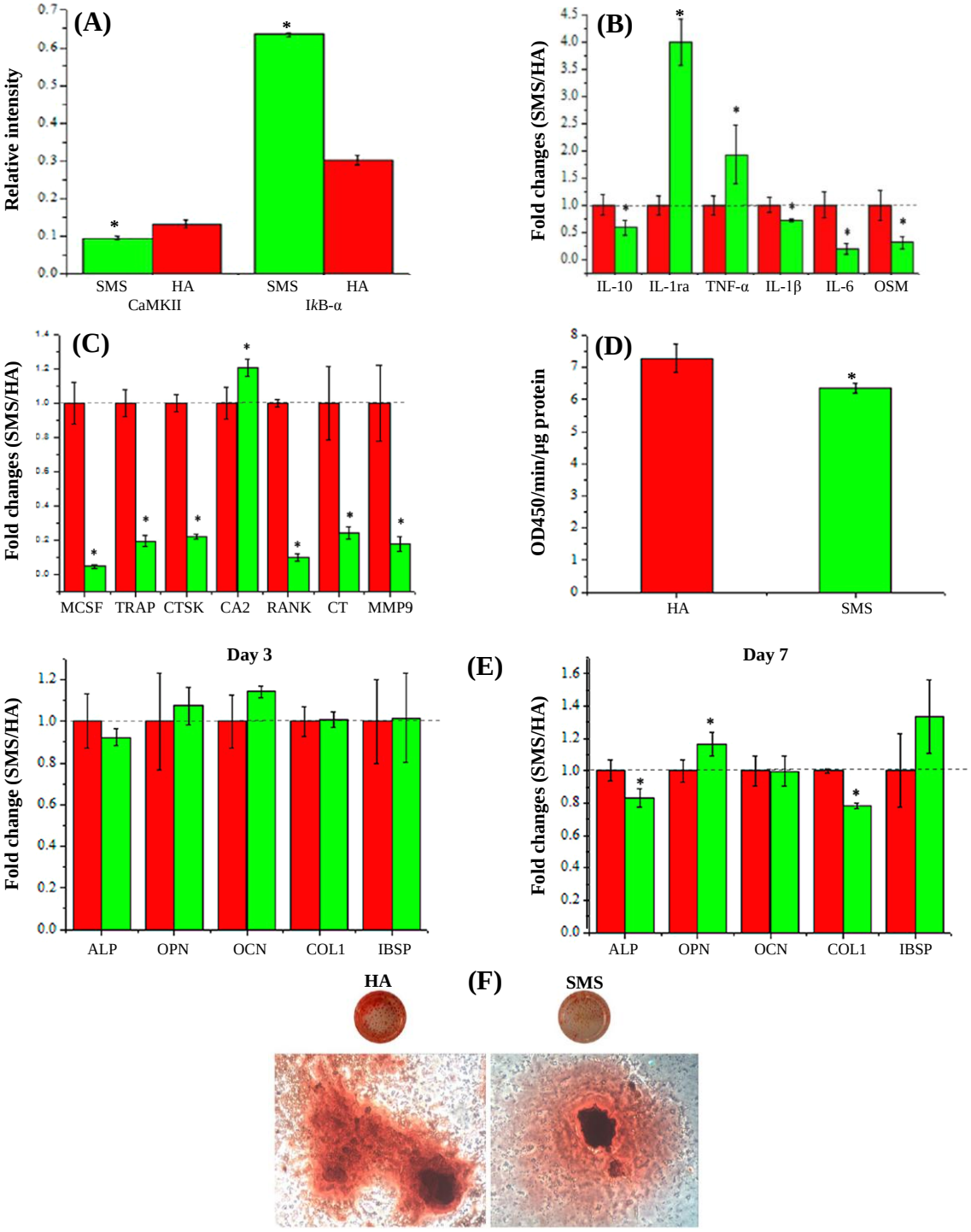

Fig. 5. The mechanism by which SMS coating hinders the inflammatory response. A significant decrease in Ca^{2+} and an increase in Mg^{2+} and Sr^{2+} concentrations inhibit the formation of fibrous capsule by Wnt and Ca^{2+} pathway (Wnt/Ca^{2+})-related genes and toll-like receptors pathway. (A) Expression of calmodulin-dependent protein kinase II (CaMKII) and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (I*k*B-α). (B) Chages of inflammation-related genes including interleukin 10 (IL-10), interleukin-1 receptor antagonist (IL-1ra), tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin 6 (IL-6) and oncostatin M (OSM). (C) the activities of osteoclastogenesis- and osteoclast-related genes, including macrophage-colony stimulating factor (MCSF), tartrate-resistant acid phosphatase (TRAP), cathepsin K (CTSK), carbonic anhydrase II (CA2), receptor activator of nuclear factor k B (RANK), calcitonin (CT) and matrix metalloproteinase-9 (MMP9). (D) ALP activities of HA and SMS coatings (E). Osteogenesis-related gene expression, including alkaline phosphatase (ALP), osteopontin (OPN), osteocalcin (OCN), collagen type I (COL1) and integrin-binding sialoprotein (IBSP) by BMSCs in days 3 and 7. (F) Bone mineralization of HA and SMS coatings. * shows significant difference (P<0.05). Reproduced with permission[42], Copyright 2014, ACS applied materials & interfaces.

In summary, all modified Ca-Si ceramic coatings show higher bonding strength compared to HA and polymeric coating such as chitosan. This high bonding strength can be mostly due to the comparable CTE between coating and substrate, their microstructure and preparation method. This silicate coating improves degradation rate and forms an apatite layer on the surface. In addition, the higher bonding strength of these coating materials is valuable for *in vivo* implant tissue integration, indicating that the stress at the implant-tissue interface is decreased, and biological stability and lifetime of the implant are improved.

This review discussed that the methods of coating preparation would lead to different bonding strength values. For example, the $CaTiSiO_5$ prepared by sol-gel spinning has shown to have a bonding strength considerably lower than that of prepared by plasma spray method. This issue indicates that different preparation methods may have influence on the properties and the performance of coatings. Also, there are few *in vivo* studies focusing on these modified coating Ti-6Al-4V substrate. In addition, post-real time evaluations such as magnetic resonance imaging are useful for better understanding of their biological performance.

CONFLICT OF INTEREST. None declared.

REFERENCES

1. Goodman SB, Gómez Barrena E, Takagi M, Konttinen YT. Biocompatibility of total joint replacements: a review. *Journal of biomedical materials research part A* 2009; **90**(2): 603-618.
2. Razavi M, Fathi M, Savabi O, Vashaee D, Tayebi L. Improvement of biodegradability, bioactivity, mechanical integrity and cytocompatibility behavior of biodegradable Mg based orthopedic implants using nanostructured bredigite ($Ca_7MgSi_4O_{16}$) bioceramic coated via ASD/EPD technique. *Annals of biomedical engineering* 2014; **42**(12): 2537-2550.
3. Branemark PI. Osseointegration and its experimental background. *The Journal of prosthetic dentistry* 1983; **50**(3): 399-410.
4. Geetha M, Singh AK, Asokamani R, Gogia AK. Ti based biomaterials, the ultimate choice for orthopaedic implants– A review. *Progress in materials science* 2009; **54**(3): 397-425.
5. Long M, Rack HJ. Titanium alloys in total joint replacement-a materials science perspective. *Biomaterials* 1998; **19**(18): 1621-1639.
6. Liu X, Chu PK, Ding C. Surface modification of titanium, titanium alloys, and related materials for biomedical applications. *Materials science and engineering: R reports* 2004; **47**(3): 49-121.
7. Okazaki Y, Gotoh E. Comparison of metal release from various metallic biomaterials *in vitro*. *Biomaterials* 2005; **26**(1): 11-21.
8. Okazaki Y, Rao S, Ito Y, Tateishi T. Corrosion resistance, mechanical properties, corrosion fatigue strength and cytocompatibility of new Ti alloys without Al and V. *Biomaterials* 1998; **19**(13): 1197-1215.
9. Fu Q, Hong Y, Liu X, Fan H, Zhang X. A hierarchically graded bioactive scaffold bonded to titanium substrates for attachment to bone. *Biomaterials* 2011; **32**(30): 7333-7346.
10. Salahinejad E, Hadianfard MJ, Macdonald DD, Sharifi Asl S, Mozafari M, Walker KJ, Rad AT, Madihally SV, Vashaee D, Tayebi L. Surface modification of stainless steel orthopedic implants by sol-gel $ZrTiO_4$ and $ZrTiO_4$-PMMA coatings. *Journal of biomedical nanotechnology* 2013; **9**(8): 1327-1335.
11. Kurtz S, Mowat F, Ong K, Chan N, Lau E, Halpern M. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. *The Journal of bone & joint surgery* 2005; **87**(7): 1487-1497.
12. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *The Journal of bone and joint surgery* 2007; **89**(4): 780-785.
13. Ramaswamy Y, Wu C, Zreiqat H. Orthopedic coating materials: considerations and applications. *Expert review of medical devices* 2009; **6**(4): 423-430.
14. Staiger MP, Pietak AM, Huadmai J, Dias G. Magnesium and its alloys as orthopedic biomaterials: a review. *Biomaterials* 2006; **27**(9): 1728-1734.
15. Zreiqat H, Howlett CR. Titanium substrata composition influences osteoblastic phenotype: *In vitro* study. *Journal of biomedical materials research* 1999; **47**(3): 360-366.
16. Zreiqat H, Howlett CR, Zannettino A, Evans P, Schulze-Tanzil G, Knabe C, Shakibaei M. Mechanisms of magnesium-stimulated adhesion of osteoblastic cells to commonly used orthopaedic implants. *Journal of biomedical materials research* 2002; **62**(2): 175-184.
17. Kim HM, Miyaji F, Kokubo T, Nakamura T. Preparation of bioactive Ti and its alloys via simple chemical surface treatment. *Journal of biomedical materials research* 1996; **32**(3): 409-417.
18. Lee BH, Do Kim Y, Shin JH, Hwan Lee K. Surface modification by alkali and heat treatments in titanium alloys. *Journal of biomedical materials research* 2002; **61**(3): 466-473.
19. Nie X, Leyland A, Matthews A, Jiang J, Meletis E. Effects of solution pH and electrical parameters on hydroxyapatite coatings deposited by a plasma-assisted electrophoresis technique. *Journal of biomedical materials research* 2001; **57**(4): 612-618.
20. Wu C, Ramaswamy Y, Gale D, Yang W, Xiao K, Zhang L, Yin Y, Zreiqat H. Novel sphene coatings on Ti-6Al-4V for orthopedic implants using sol–gel method. *Acta biomaterialia* 2008; **4**(3): 569-576.
21. Liu X, Ding C, Chu PK. Mechanism of apatite formation on wollastonite coatings in simulated body

fluids. *Biomaterials* 2004; **25**(10): 1755-1761.
22. Zheng X, Huang M, Ding C. Bond strength of plasma-sprayed hydroxyapatite/Ti composite coatings. *Biomaterials* 2000; **21**(8): 841-849.
23. Braem A, Mattheys T, Neirinck B, Ceh M, Novak S, Schrooten J, Van der Biest O, Vleugels. Bioactive glass–ceramic coated titanium implants prepared by electrophoretic deposition. *Materials science and engineering: C* 2012; **32**(8): 2267-2273.
24. Singh I, Kaya C, Shaffer M, Thomas B, Boccaccini A. Bioactive ceramic coatings containing carbon nanotubes on metallic substrates by electrophoretic deposition. *Journal of materials science* 2006; **41**(24): 8144-8151.
25. Lin S, LeGeros RZ, LeGeros JP. Adherent octacalciumphosphate coating on titanium alloy using modulated electrochemical deposition method. *Journal of Biomedical materials research part A* 2003; **66**(4): 819-828.
26. Narayanan R, Seshadri SK, Kwon TY, Kim KH. Calcium phosphate-based coatings on titanium and its alloys. *Journal of biomedical materials research part B applied biomaterials* 2008; **85**(1): 279-299.
27. Nagano M, Nakamura T, Kokubo T, Tanahashi M, Ogawa M. Differences of bone bonding ability and degradation behavior in vivo between amorphous calcium phosphate and highly crystalline hydroxyapatite coating. *Biomaterials* 1996; **17**(18): 1771-1777.
28. Lin DY, Wang XX. A novel method to synthesize hydroxyapatite coating with hierarchical structure. *Colloids and surfaces B biointerfaces* 2011; **82**(2): 637-640.
29. Liu X, Tao S, Ding C. Bioactivity of plasma sprayed dicalcium silicate coatings. *Biomaterials* 2002; **23**(3): 963-968.
30. Hench LL. Bioceramics: from concept to clinic. *Journal of the american ceramic society* 1991; **74**(7): 1487-1510.
31. Oonishi H, Hench LL, Wilson J, Sugihara F, Tsuji E, Kushitani S, Iwaki H. Comparative bone growth behavior in granules of bioceramic materials of various sizes. *Journal of biomedical materials research* 1999; **44**(1): 31-43.
32. Bauer TW, Geesink R, Zimmerman R, McMahon JT. Hydroxyapatite-coated femoral stems. Histological analysis of components retrieved at autopsy. *The Journal of bone and joint surgery* 1991; **73**(10): 1439-1452.
33. Kweh SW, Khor KA, Cheang P. An *in vitro* investigation of plasma sprayed hydroxyapatite (HA) coatings produced with flame-spheroidized feedstock. *Biomaterials* 2002; **23**(3): 775-785.
34. Xue W, Liu X, Zheng X, Ding C. Plasma-sprayed diopside coatings for biomedical applications. *Surface and coatings technology* 2004; **185**(2-3): 340-345.
35. Wu C, Ramaswamy Y, Liu X, Wang G, Zreiqat H. Plasma-sprayed $CaTiSiO_5$ ceramic coating on Ti-6Al-4V with excellent bonding strength, stability and cellular bioactivity. *Journal of the royal society interface* 2009; **6**(31): 159-168.
36. Khor KA, Gu YW, Pan D, Cheang P. Microstructure and mechanical properties of plasma sprayed HA/YSZ/Ti–6Al–4V composite coatings. *Biomaterials* 2004; **25**(18): 4009-4017.
37. McPherson R, Gane N, Bastow T. Structural characterization of plasma-sprayed hydroxylapatite coatings. *Journal of materials science materials in medicine* 1995; **6**(6): 327-334.
38. Breme J, Zhou Y, Groh L. Development of a titanium alloy suitable for an optimized coating with hydroxyapatite. *Biomaterials* 1995; **16**(3): 239-244.
39. Lacefleld WR, Hench LL. The bonding of Bioglass® to a cobalt-chromium surgical implant alloy. *Biomaterials* 1986; **7**(2): 104-1088.
40. Oliva A, Salerno A, Locardi B, Riccio V, Della Ragione F, Iardino P, Zappia V. Behavior of human osteoblasts cultured on bioactive glass coatings. *Biomaterials* 1998; **19**(11): 1019-1025.
41. Bloyer DR, Gomez-Vega JM, Saiz E, McNaney JM, Cannon RM, Tomsia AP. Fabrication and characterization of a bioactive glass coating on titanium implant alloys. *Acta materialia* 1999; **47**(15-16): 4221-4224.
42. Wu C, Chen Z, Yi D, Chang J, Xiao Y. Multidirectional effects of Sr, Mg and Si-containing bioceramic coatings with high bonding strength on inflammation, osteoclastogenesis and osteogenesis. *ACS applied materials & interfaces* 2014; **6**(6): 4264-4267
43. Ni S, Chang J, Chou L, Zhai W. Comparison of osteoblast-like cell responses to calcium silicate and tricalcium phosphate ceramics *in vitro*. *Journal of biomedical materials research Part B applied biomaterials* 2007; **80**(1): 174-183.
44. Sarmento C, Luklinska ZB, Brown L, Anseau M, De Aza PN, De Aza S, Hughes FJ, McKay IJ. *In vitro* behavior of osteoblastic cells cultured in the presence of pseudowollastonite ceramic. *Journal of biomedical materials research Part A* 2004; **69**(2): 351-358.
45. Xu S, Lin K, Wang Z, Chang J, Wang L, Lu J, Ning C. Reconstruction of calvarial defect of rabbits using porous calcium silicate bioactive ceramics. *Biomaterials* 2008; **29**(17): 2588-2596.
46. Ning C, Zhou Y, Chen L, Lin K. Antibacterial activity of silicate bioceramics. *Journal of Wuhan University of Technology-Mater Sci Ed* 2011; **26**(2): 226-230.
47. Liu N, Fan W, Wu C, Fan B. The interactions of Mg^{2+}/Zn^{2+}-containing silicate materials with stem cells and bacteria. *Materials letters* 2013; **112**: 105-108.
48. Yi D, Wu C, Ma X, Ji H, Zheng X, Chang J. Preparation and in vitro evaluation of plasma-sprayed bioactive akermanite coatings. *Biomedical materials* 2012; **7**(6): 065004.
49. Li K, Yu J, Xie Y, Huang L, Ye X, Zheng X. Chemical stability and antimicrobial activity of plasma sprayed bioactive Ca2ZnSi2O7 coating. *Journal of materials science materials in medicine* 2011; **22**(12): 2781-2789.
50. Ramaswamy Y, Wu C, Zhou H, Zreiqat H. Biological response of human bone cells to zinc-modified Ca–Si-based ceramics. *Acta biomaterialia* 2008; **4**(5): 1487-1497.
51. Mohammadi H, Sepantafar M, Ostadrahimi A. The Role

of Bioinorganics in Improving the Mechanical Properties of Silicate Ceramics as Bone Regenerative Materials. *Journal of ceramic science and technology* 2015; **6**(1): 1-8.
52. Mohammadi H, Hafezi M, Nezafati N, Heasarki S, Nadernezhad A, Ghazanfari SMH, Sepantafar M. Bioinorganics in Bioactive Calcium Silicate Ceramics for Bone Tissue Repair: Bioactivity and Biological Properties. *Journal of ceramic science and technology* 2013; **5**(1): 1-12.
53. Wu C, Ramaswamy Y, Chang J, Woods J, Chen Y, Zreiqat H. The effect of Zn contents on phase composition, chemical stability and cellular bioactivity in Zn-Ca-Si system ceramics. *Journal of biomedical materials research part B, applied biomaterials* 2008; **87**(2): 346-353.
54. Wu C, Chang J. A review of bioactive silicate ceramics. *Biomedical materials* 2013; **8**(3): 032001.
55. Zhang W, Wang G, Liu Y, Zhao X, Zou D, Zhu C, Jin Y, Huang Q, Sun J, Liu X, Jiang X, Zreigat H. The synergistic effect of hierarchical micro/nano-topography and bioactive ions for enhanced osseointegration. *Biomaterials* 2013; **34**(13): 3184-3195.
56. Fathi MH, Meratian M, Razavi M. Novel Magnesium-Nanofluorapatite Metal Matrix Nanocomposite with Improved Biodegradation Behavior. *Journal of biomedical nanotechnology* 2011; **7**(3): 441-445.
57. Razavi M, Fathi M, Meratian M. Microstructure, mechanical properties and bio-corrosion evaluation of biodegradable AZ91-FA nanocomposites for biomedical applications. *Materials science and engineering: A* 2010; **527**(26): 6938-6944.
58. Razavi M, Fathi M, Meratian M. Bio-corrosion behavior of magnesium-fluorapatite nanocomposite for biomedical applications. *Materials letters* 2010; **64**(22): 2487-2490.
59. Razavi M, Fathi M, Meratian M. Fabrication and characterization of magnesium–fluorapatite nanocomposite for biomedical applications. *Materials characterization* 2010; **61**(12): 1363-1370.
60. Yang L, Zhang E. Biocorrosion behavior of magnesium alloy in different simulated fluids for biomedical application. *Materials science and engineering: C* 2009; **29**(5): 1691-1696.
61. Oh IH, Nomura N, Chiba A, Murayama Y, Masahashi N, Lee BT, Hanada S. Microstructures and bond strengths of plasma-sprayed hydroxyapatite coatings on porous titanium substrates. *Journal of materials science materials in medicine* 2005; **16**(7): 635-640.
62. Song Y, Shan D, Han E. Electrodeposition of hydroxyapatite coating on AZ91D magnesium alloy for biomaterial application. *Materials letters* 2008; **62**(17): 3276-3279.
63. Wei J, Heo SJ, Kim DH, Kim SE, Hyun YT, Shin JW. Comparison of physical, chemical and cellular responses to nano- and micro-sized calcium silicate/poly(epsilon-caprolactone) bioactive composites. *Journal of the royal society, interface the royal society* 2008; **5**(23): 617-630.
64. Xu JL, Liu F, Wang FP, Yu DZ, Zhao LC. The corrosion resistance behavior of Al_2O_3coating prepared on NiTi alloy by micro-arc oxidation. *Journal of alloys and compounds* 2009; **472**(1-2): 276-280.
65. Kwok CK, Wong PK, Cheng FT, Man HC. Characterization and corrosion behavior of hydroxyapatite coatings on Ti6Al4V fabricated by electrophoretic deposition. *Applied surface science* 2009; **255**(13): 6736-6744.
66. Hoppe A, Guldal NS, Boccaccini AR. A review of the biological response to ionic dissolution products from bioactive glasses and glass-ceramics. *Biomaterials* 2011; **32**(11): 2757-2774.
67. Wozniak MA, Chen CS. Mechanotransduction in development: a growing role for contractility. *Nature reviews molecular cell biology* 2009; **10**(1): 34-43.
68. Anselme K. Osteoblast adhesion on biomaterials. *Biomaterials* 2000; **21**(7): 667-681.
69. Siebers MC, ter Brugge PJ, Walboomers XF, Jansen JA. Integrins as linker proteins between osteoblasts and bone replacing materials. A critical review. *Biomaterials* 2005; **26**(2): 137-146.
70. Roach P, Eglin D, Rohde K, Perry CC. Modern biomaterials: a review - bulk properties and implications of surface modifications. *Journal of materials science materials in medicine* 2007; **18**(7): 1263-1277.
71. Ni S, Lin K, Chang J, Chou L. Beta-CaSiO3/beta-$Ca_3(PO_4)_2$ composite materials for hard tissue repair: *in vitro* studies. *Journal of biomedical materials research part A* 2008; **85**(1): 72-82.
72. Wilson CJ, Clegg RE, Leavesley DI, Pearcy MJ. Mediation of biomaterial-cell interactions by adsorbed proteins: a review. *Tissue engineering* 2005; **11**(1-2): 1-18.
73. Bohner M, Galea L, Doebelin N. Calcium phosphate bone graft substitutes: Failures and hopes. *Journal of the european ceramic society* 2012; **32**(11): 2663-2671.
74. Liu X, Morra M, Carpi A, Li B. Bioactive calcium silicate ceramics and coatings. *Biomedicine and pharmacotherapy* 2008; **62**(8): 526-529.
75. Liu X, Ding C, Wang Z. Apatite formed on the surface of plasma-sprayed wollastonite coating immersed in simulated body fluid. *Biomaterials* 2001; **22**(14): 2007-2012.
76. Xue W, Liu X, Zheng X, Ding C. In vivo evaluation of plasma-sprayed wollastonite coating. *Biomaterials* 2005; **26**(17): 3455-3460.
77. Xie Y, Zheng X, Ding C, Zhai W, Chang J, Ji H. Preparation and Characterization of CaO-ZrO_2-SiO_2 Coating for Potential Application in Biomedicine. *J therm spray tech* 2009; **18**(4): 678-685.
78. Hayashi H, Saitou T, Maruyama N, Inaba H, Kawamura K, Mori M. Thermal expansion coefficient of yttria stabilized zirconia for various yttria contents. *Solid state ionics* 2005; **176**(5-6): 613-619.
79. Yang F, Xie Y, Li H, Tang T, Zhang X, Gan Y, Zheng X, Dai K. Human bone marrow-derived stromal cells cultured with a plasma sprayed CaO-ZrO_2-SiO_2 coating. *Journal of biomedical materials research part B: applied biomaterials* 2010; **95**(1): 192-201.
80. Liang Y, Xie Y, Ji H, Huang L, Zheng X. Excellent

stability of plasma-sprayed bioactive $Ca_3ZrSi_2O_9$ ceramic coating on Ti–6Al–4V. *Applied surface science* 2010; **256**(14): 4677-4681.
81. Tsui YC, Doyle C, Clyne TW. Plasma sprayed hydroxyapatite coatings on titanium substrates Part 2: optimisation of coating properties. *Biomaterials* 1998; **19**(22): 2031-2043.
82. Ning C, Wang Y, Chen X, Zhao N, Ye J, Wu G. Mechanical performances and microstructural characteristics of plasma-sprayed bio-functionally gradient HA–ZrO2-Ti coatings. *Surface and coatings technology* 2005; **200**(7): 2403-2408.
83. Yi D, Wu C, Ma B, Ji H, Zheng X, Chang J. Bioactive bredigite coating with improved bonding strength, rapid apatite mineralization and excellent cytocompatibility. *Journal of biomaterials applications* 2013; **28**(9): 1343-1353.
84. Liu X, Ding C. Characterization of plasma sprayed wollastonite powder and coatings. *Surface and coatings technology* 2002; **153**(2): 173-177.
85. Wu C, Chang J, Zhai W, Ni S. A novel bioactive porous bredigite ($Ca_7MgSi_4O_{16}$) scaffold with biomimetic apatite layer for bone tissue engineering. *Journal of materials science materials in medicine* 2007; **18**(5): 857-864.
86. Chou YF, Huang W, Dunn JC, Miller TA, Wu BM. The effect of biomimetic apatite structure on osteoblast viability, proliferation, and gene expression. *Biomaterials* 2005; **26**(3): 285-295.
87. Choi J, Bogdanski D, Köller M, Esenwein SA, Müller D, Muhr G, Epple M. Calcium phosphate coating of nickel–titanium shape-memory alloys. Coating procedure and adherence of leukocytes and platelets. *Biomaterials* 2003; **24**(21): 3689-3696.
88. Thian ES, Huang J, Best SM, Barber ZH, Brooks RA, Rushton N, Bonfield W. The response of osteoblasts to nanocrystalline silicon-substituted hydroxyapatite thin films. *Biomaterials* 2006; **27**(13): 2692-2698.
89. Botelho C, Brooks R, Best S, Lopes MA, Santos JD, Rushton N, Bonfield W. Human osteoblast response to silicon-substituted hydroxyapatite. *Journal of biomedical materials research Part A* 2006; **79**(3): 723-730.
90. Liu Q, Cen L, Yin S, Chen L, Liu G, Chang J, Cui L. A comparative study of proliferation and osteogenic differentiation of adipose-derived stem cells on akermanite and β-TCP ceramics. *Biomaterials* 2008; **29**(36): 4792-4799.
91. Liu G, Wu C, Fan W, Miao X, Sin DC, Crawford R, Xiao Y. The effects of bioactive akermanite on physiochemical, drug-delivery, and biological properties of poly (lactide-co-glycolide) beads. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 2011; **96**(2): 360-368.
92. Gomez-Vega JM, Saiz E, Tomsia AP. Glass-based coatings for titanium implant alloys. *Journal of biomedical materials research* 1999; **46**(4): 549-559.
93. Wang G, Lu Z, Liu X, Zhou X, Ding C, Zreiqat H. Nanostructured glass-ceramic coatings for orthopaedic applications. *Journal of the royal society interface the royal society* 2011; **8**(61): 1192-1203.
94. Haussühl S, Liebertz J. Elastic and thermoelastic properties of synthetic $Ca_2MgSi_2O_7$ (åkermanite) and $Ca_2ZnSi_2O_7$ (hardystonite). *Physics and chemistry of minerals* 2004; **31**(8): 565-567.
95. Li K, Xie Y, Huang L, Ji H, Zheng X. Antibacterial mechanism of plasma sprayed $Ca_2ZnSi_2O_7$ coating against *Escherichia coli*. *Journal of materials science materials in medicine* 2013; **24**(1): 171-178.
96. Ramaswamy Y, Wu C, Dunstan CR, Hewson B, Eindorf T, Anderson GI, Zreiqat H. Sphene ceramics for orthopedic coating applications: An *in vitro* and *in vivo* study. *Acta biomaterialia* 2009; **5**(8): 3192-3204.
97. Pilous V, Musil J. Bonding of plasma sprayed coatings with the substrate material. *Welding international* 1988; **2**(10): 934-938.
98. Khor K, Yip C, Cheang P. Ti-6Al-4V/hydroxyapatite composite coatings prepared by thermal spray techniques. *Journal of thermal spray technology* 1997; **6**(1): 109-115.
99. Mohammadi H, Hafezi M, Hesaraki S, Sepantafar M. Preparation and characterization of Sr-Ti-hardystonite (Sr-Ti-HT) nanocomposite for bone repair application. *Nanomedicine* journal 2015; **2**(3): 203-210.
100. Chen Z, Yi D, Zheng X, Chang J, Wu C, Xiao Y. Nutrient element-based bioceramic coatings on titanium alloy stimulating osteogenesis by inducing beneficial osteoimmmunomodulation. *Journal of materials chemistry B* 2014; **2**(36): 6030-6043.
101. De A. Wnt/Ca^{2+} signaling pathway: a brief overview. *Acta biochimica et biophysica sinica* 2011; **43**(10): 745-756.
102. Römer P, Desaga B, Proff P, Faltermeier A, Reicheneder C. Strontium promotes cell proliferation and suppresses IL-6 expression in human PDL cells. *Annals of anatomy-anatomischer anzeiger* 2012; **194**(2): 208-211.
103. Buache E, Velard F, Bauden E, Guillaume C, Jallot E, Nedelec JM, Laurent-Maquin D, Laquerriere P. Effect of strontium-substituted biphasic calcium phosphate on inflammatory mediators production by human monocytes. *Acta biomater* 2012; **8**(8): 3113-3119.
104. Sugimoto J, Romani AM, Valentin-Torres AM, Luciano AA, Ramirez Kitchen CM, Funderburg N, Mesiano S, Bernstein HB. Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism. *Journal of immunology (Baltimore, Md : 1950)* 2012; **188**(12): 6338-6346.
105. Bonnelye E., Chabadel A, Saltel F, Jurdic, P. Dual effect of strontium ranelate: Stimulation of osteoblast differentiation and inhibition of osteoclast formation and resorption *in vitro*. *Bone* 2008; **42**(1): 129-138.
106. Razavi M, Fathi M, Savabi O, Hashemi Beni B, Vashaee D, Tayebi L. Surface microstructure and in vitro analysis of nanostructured akermanite ($Ca_2MgSi_2O_7$) coating on biodegradable magnesium alloy for biomedical applications. *Colloids and surfaces b biointerfaces* 2014; **117**: 432-440.
107. Besra L, Liu M. A review on fundamentals and applications of electrophoretic deposition (EPD).

Progress in materials science 2007; **52**(1): 1-61.
108. Shang W, Chen B, Shi X, Chen Y, Xiao X. Electrochemical corrosion behavior of composite MAO/sol–gel coatings on magnesium alloy AZ91D using combined micro-arc oxidation and sol–gel technique. *Journal of alloys and compounds* 2009; **474**(1-2): 541-545.
109. Lei T, Ouyang C, Tang W, Li LF, Zhou LS. Enhanced corrosion protection of MgO coatings on magnesium alloy deposited by an anodic electrodeposition process. *Corrosion science* 2010; **52**(10): 3504-3508.
110. Kharaziha M, Fathi MH. Synthesis and characterization of bioactive forsterite nanopowder. *Ceramics international* 2009; **35**(6): 2449-2454.
111. Bumgardner JD, Wiser R, Gerard PD, Bergin P, Chestnutt B, Marin M, Ramsey V, Elder SH, Gilbert JA. Chitosan: potential use as a bioactive coating for orthopaedic and craniofacial/dental implants. *Journal of biomaterials science polymer edition* 2003; **14**(5): 423-438.