



Review of the Role of Calcium Silicate Ceramics for Bone Tissue Repair

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ABSTRACT

Bioinorganic science and the utilization of metal ions in the synthesis and design of new materials have received considerable attention in relation to their use as new biomaterials. One of the important roles of metal ions is to control the characteristics of the resulting biomaterials, namely their biological and chemical properties. To date, main group metal ions and transition metals have been used in the fabrication process of silicate and phosphate-based ceramics. Metal ions are used to modify their chemical composition and structure to overcome the shortcomings of silicate and phosphate-based ceramics. Calcium silicate (CaSiO₃, CS) ceramics are biocompatible and bioactive. In this review, we consider the apatite-forming ability and 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, all of them may be good candidates for bone tissue regeneration.

Keywords: bioceramics, calcium silicate, bone tissue

I. INTRODUCTION

Bone tissue engineering has now been developed by several researchers, related to its use in the medical field. Many patients need bone regeneration that is damaged due to accidents or illness every year. (Cho, Choi, Lee, Kim, & Cho, 2019).. Bone is the second most commonly transplanted tissue, with approximately four million operations performed each year using different bone alternatives (Turnbull et al., 2018).. Bone tissue consists of a unique extracellular matrix composed of inorganic materials (Jodati, Yılmaz, & Evis, 2020).. Bioinorganic as a supporter of bone formation has several advantages, such as being able to eradicate the side effects and complications of hormones (Mohammadi et al., 2014).. One of the bioinorganic materials that is widely applied for bone repair is CS ceramics. However, CS ceramics have weaknesses related to low mechanical strength and are sensitive to increased pH values which affect their degradation ability which can be deadly to cells. (Srinath, Abdul Azeem, & Venugopal Reddy, 2020)..

A study showed that CS-induced apatite formation in body fluids contains inorganic ions similar to the concentration of human extracellular matrix and is strongly bound to host bone tissue in vivo. (De Aza, Aza, Peña, & Aza, 2018) and the rate of CS apatite formation is faster than bioactive glass (Siriphannon, Kameshima, Yasumori, Okada, & Hayashi, 2002).. In recent years, modification of CS ceramics using metal ions has been carried out to improve their biomedical and mechanical properties. With the Ca-Si-X system (where X can be Mg, Zn, Ti and Zr), it has been found for bone tissue regeneration (Jodati et al., 2020; Y.-H. Lin et al., 2022; Xu, Meng, Li, & Zhu, 2021).. These materials have good osteoinductivity and osteoconductivity (Zheng et al., 2021). A new class of ion-doped bioactive CS with a wide range of compositions has been developed. For this reason, the aim of this review is to investigate the biological properties of ion-doped CS ceramics from various studies.

II. CS Ceramic as Bone Tissue Repair

The utilization of CS-based ceramic candidates as bone tissue repair materials must be studied regarding a thorough understanding of the physiological role of calcium and silica ions in bone metabolism.

The human body contains about 2% Ca of which 98% is found in bone. Body fluids and cells contain 10 to 15 mg per 100 mg. Ca is present in the active regions of natural bone and plays an important role in blood vessels and bone growth. (Pravina, Sayaji, ..., & 2013, 2013). It has been found that low Ca concentrations of 2 - 4 mmol support osteoblast proliferation and differentiation, and medium concentrations of 6 - 8 mmol support extracellular matrix (ECM) mineralization, whereas higher Ca concentrations greater than 10 mmol were shown to be toxic to the cells (Maeno et al., 2005). (Maeno et al., 2005). In addition, extracellular calcium plays a biological role in regulating bone restoration independent of hormones by stimulation of cation-sensing receptors (Marie, 2010). For example, extracellular Ca can enhance the utility of insulin-like growth factor (IGF) II, which explicitly regulates osteoblast proliferation. Extracellular Ca concentration can also increase osteoblast glutamate release (Midha et al., 2013).

III. CS ceramic composition

A wide variety of biomaterials are used to produce scaffolds for BTEs (Civinini et al., 2012).. Bioceramics, polymers (Gunatillake, Adhikari, & Gadegaard, 2003), and composite scaffolds (Turnbull et al., 2018)(Alvarez-Urena, Kim, Bhattacharyya, & Ducheyne, 2017) may find more applications than conventional non-degradable metal biomaterials (Roseti et al., 2017). However, metallic scaffolds, such as Ti and its alloys, which are commonly used in load-bearing applications to provide mechanical and structural support e.g. in joint arthroplasty and fractures of long bones and vertebrae, are also investigated in BTEs (S. Wang et al., 2017). (S. Wang et al., 2019)(Chen et al., 2017).

Polymers can be classified into two categories: natural and synthetic. Polycaprolactone (PCL), polylactic acid (PLA), polypropylene fumarate (PPF), poly-lactic-co-glycolic acid (PLGA) and polyether ether ketone (PEEK) are just a few examples of synthetic polymers while, collagen, hyaluronic acid, silk, and chitosan are considered as well-known natural polymers (Dhandayuthapani, Yoshida, Maekawa, & Kumar, 2011)(Fomby et al., 2010)(Jiaolong Wang et al., 2016)(Bhattacharjee et al., 2017). The main disadvantage of polymers is their low mechanical properties which limit their application in load-bearing tissues such as bone (Woodruff & Hutmacher, 2010)(Stratton, Shelke, Hoshino, Rudraiah, & Kumbar, 2016).

Natural polymers consisting of proteins (e.g. collagen, gelatin, and fibrinogen), polysaccharides (e.g. glycosaminoglycans) and polynucleotides (e.g. DNA and RNA) show better osteoinductivity than synthetics due to their similarity to native ECMs, however, their mechanical properties are not good enough and their biodegradability is poorly controlled. (Haugen, Lyngstadaas, Rossi, & Perale, 2019).. In addition, polymeric carriers can be used, for example, for effective delivery of drugs, metabolic supplements, or body growth factors. Natural polymers have opposite charges compared to bioactive molecules, which leads to ionic interactions between them. This creates a strong relationship that can protect the molecules in a stable form and can affect the release process. A combination of natural and synthetic polymers may be preferred to regulate the sustained release of molecules from the composite. (Rao, Harini, Shadamarshan, Balangadharan, & Selvamurugan, 2018)..

Bioceramics, both of natural and synthetic origin, are very promising biomaterials that are often used in BTE applications [26]. The range of bioceramics has been extended from bioactive amorphous glasses (BG), crystalline ceramics such as HAp and tricalcium phosphate (TCP), to calcium silicates. Their advantages can be listed as chemical composition similar to inorganic parts of bone tissue and consequent biocompatibility, high compressive strength, bioactivity, osteoconductivity, as well as possible osteoinductivity. (LeGeros, 2008)(Ma, Feng, Chang, & Wu, 2018). However, being brittle due to primary ionic and/or covalent bonds, and low ductility are the main drawbacks of bioceramics that partially limit their application for non-load bearing and filling of bone defects, such as: as well as metallic implant coatings. (Dorozhkin, 2018). Some fabrication examples of ion-doped CS ceramics are shown in Table 1.

Table 1. Fabrication of ion-doped CS ceramics

Ceramic	Stoichiometric Formula	Fabrication method	Sintered temperature (°C)	Ref.
α -CS	CaO-SiO ₂	Chemical precipitation	1250	(K. Lin et al., 2005)
β -CS	CaO-SiO ₂	Chemical precipitation	1100	(K. Lin et al., 2013)
Sr- α -CaSiO ₃ (Sr- α -CS)	xSrO-(1-x)CaO-SiO ₂ ; x = 0.01~0.10	Chemical precipitation	1250	[47]

Sr-β-CaSiO ₃ (Sr-β-CS)	xSrO-(1 - x)CaO-SiO ₂ ; x = 0.10	Chemical precipitation	1090	(Wu, Ramaswamy, Kwik, & Zreiqat, 2007)
Akermanite (AK)	2CaO-MgO-2SiO ₂	Sol-gel	1370	(Wu, Chang, Ni, & Wang, 2006)
Co-Akermanite (Co-AK)	2CaO-CoO-2SiO ₂	Sol-gel	1200	(Tian, Han, Ma, Wu, & Chang, 2015)
Sr-Bag (Sr-Bag)	xSrO-(3-x)CaO-ZrO ₂ -2SiO ₂ , x = 0.1, 0.75	Solid-state	1400	(Schumacher et al., 2015)

IV. Effect of chemical stability on the formation of CS apatite ceramics

Bioactive materials can generally bind directly to bone and can be considered as bone repair materials in clinical applications. (AL-AMLEH, LYONS, & SWAIN, 2010). There are two mechanisms of apatite formation on the surface of materials based on immersion in SBF. One is the release of some ions from the material that form a negative charge on the surface and the other is the specific microstructure at the micro- and nano-scale to provide nucleation sites (Papynov et al., 2010). (Papynov et al., 2017).. In bone implant applications CaO and SiO₂ are required for apatite formation. The apatite layer should have low crystallinity and a composition similar to the bone mineral phase (Wu et al., 2006). Bone-like apatite stimulates protein signaling and cells to initiate the sequence of events that lead to bone formation. The HA layer grows through the reaction of Ca, phosphate (PO₄³⁻) and hydroxide (OH⁻) ions and is sometimes integrated with carbonate anions (CO₃²⁻). The higher formation rate of apatite layer is related to the surface dissolution rate. The mechanism of apatite formation ability consists of several stages. First, calcium ions are released from the surface, at a later stage many silanol (Si-OH) groups are formed on the surface. These Si-OH groups make apatite nucleation heterogeneous and Ca ions increase the ionic activity and nucleation of apatite. When apatite nuclei are formed on the surface, they grow spontaneously using calcium phosphate (CaP) ions from SBF (Fig. 2). (Xu et al., 2021).

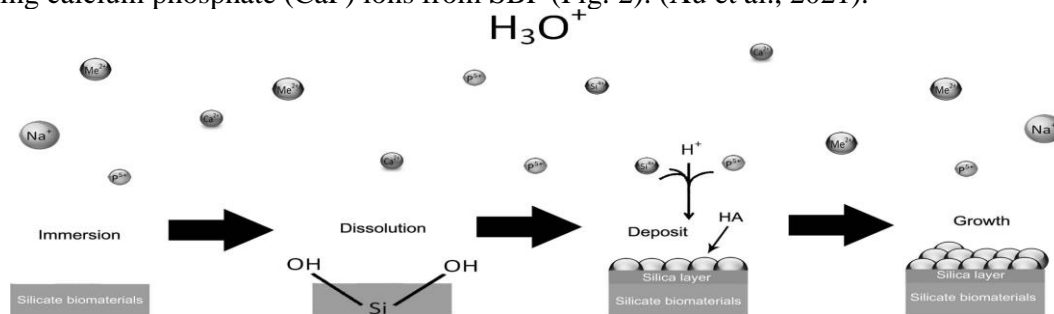


Figure 2. Mechanism of ceramic apatite formability

The apatite-forming ability in CS ceramics is largely related to the high reactivity, which leads to favorable Ca release and increased pH value in SBF 4. However, the biodegradation of wollastonite (the base compound of CS ceramics) is too fast. Another factor that might influence the degradation properties of ceramics is structure (Papynov et al., 2017). Wollastonite has a triclinic structure. The initial exchange of alkali ions 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 (No, Li, et al., 2017).. As time passes, the apatite layer formed becomes thicker due to the decrease in phosphorus (P) concentration to stabilize the pH value through inhibition of ion exchange. Apatite formation ability in SBF and chemical stability are usually considered as contradictory factors and obtaining both simultaneously is usually difficult. The apatite formation ability is directly related to the dissolution of the material and the apatite formation rate decreases with decreasing

dissolution of the bioactive glass. The pH value is one of the factors that inhibit cell proliferation. This parameter has a dual effect on cell metabolism and affects cell proliferation. High dissolution and degradation rates of CS ceramics result in high pH values in the environment, indicating their chemical instability, which is lethal to cells and inhibits cell growth⁸. Thus, their osseointegration ability is affected. There are three routes to control the environmental pH of biomaterials including composition, ion doping (discussed in this review) and surface modification. Lin et al. reported that HA/wollastonite composite has a suitable dissolution rate. Zhao et al. showed that PLGA coated on the surface of CS scaffolds improved chemical stability. It should be noted that bone is also known as biological apatite which is not pure HA and consists of Zn and Sr ions that can be replaced by different cations present in the structure of biological apatite (Hu et al., 2016). Different CS ceramics have variable apatite-forming ability during immersion in SBF¹¹⁸. Apatite formation in CS ceramics is directly related to their chemical composition and dissolution. For example, hardystonite has no obvious apatite formation and dissolution is quite slow. In contrast, akermanite shows good apatite formation. These apatite layers have different morphologies related to different chemical composition morphologies (Wu, 2018). 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 (Wu, 2013). All the above-mentioned issues indicate that metal ions play an important role in the chemical stability and apatite formation of CS ceramics.

V. CONCLUSION AND FUTURE PERSPECTIVES

CS ceramics represent a new class of bioactive ceramics with a unique set of properties, which make them suitable for use as synthetic bone substitutes with the potential to produce improved results compared to existing ceramic materials. The $x\text{CaO}-y\text{SiO}_2$ system is highly versatile, allowing doping with various ions and oxides to form different CS ceramics with customized properties depending on (1) the stoichiometric composition; (2) the fabrication method; and (3) the role of CS in the composite system. A number of CS-based composites have demonstrated properties that meet the structural, mechanical, and biological requirements for bone regeneration at load-bearing defect sites, such as akermanite, baghdadite, Sr-hardystonite and Sr-HT-Gahnite. To encourage the utilization of CS ceramics into clinical use as solid implants or scaffolds, composites, and coatings, future investigations should focus on understanding long-term biological interactions with CS in an in vivo setting. CS-based implants intended for clinical use should be tested in animal models with bone defects that have the same structure and characteristics as those found in humans. When evaluating outcomes, it will be important to clarify the interaction of bone-related cells with CS and the pathways involved in generating an enhanced regenerative response. Long-term studies will be required to monitor implant degradation and bone remodeling over time and ensure restoration of native bone architecture. In addition, the antibacterial activity of certain CS can be harnessed to produce better implants that minimize the risk of infection. Such investigations will accelerate the development of CS as the next generation of synthetic bone substitutes.

V. REFERENCES

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