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Review

Hydroxyapatites enriched in silicon – Bioceramic materials for biomedical and pharmaceutical applications

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ABSTRACT

Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, abbreviated as HA) plays a crucial role in implantology, dentistry and bone surgery. Due to its considerable similarity to the inorganic fraction of the mineralized tissues (bones, enamel and dentin), it is used as component in many bone substitutes, coatings of metallic implants and dental materials. Biomaterial engineering often takes advantage of HA capacity for partial ion substitution because the incorporation of different ions in the HA structure leads to materials with improved biological or physico-chemical properties. The objective of the work is to provide an overview of current knowledge about apatite materials substituted with silicon ions. Although the exact mechanism of action of silicon in the bone formation process has not been fully elucidated, research has shown beneficial effects of this element on bone matrix mineralization as well as on collagen type I synthesis and stabilization. The paper gives an account of the functions of silicon in bone tissue and outlines the present state of research on synthetic HA containing silicate ions (Si-HA). Finally, methods of HA production as well as potential and actual applications of HA materials modified with silicon ions are discussed.

1. Introduction

In terms of its global distribution, silicon (Si) is second only to oxygen, accounting for approx. 26–29% of the earth's crust. It does not occur in pure form in nature due to its high affinity for oxygen and hydrogen. The most abundant silicon compound is silica or silicon dioxide (SiO_2). In the human body, silicon is one of the trace elements, coming after zinc and iron [1,2]. The bioavailable forms of silicon include silicic acids, as well as soluble sodium and potassium metasilicates (Na_2SiO_3, K_2SiO_3), which release orthosilicic acid in the stomach in the presence of hydrochloric acid. In addition, silica gel releases some orthosilicic acid upon contact with body fluids. The serum concentration of silicon amounts to 10–30 μg/dL. This element is present in all tissues, with the highest content found in connective tissues, including the aorta, trachea, bones and skin. The concentration of Si in the hair and fingernails ranges from 1 to 10 ppm, while that in bones amounts to as much as 100–150 ppm dry weight [1–6]. Silicon distribution in the body is linked to its biological activity, especially in terms of the functions of connective tissues, and in particular bones. Silicon has been found to affect the condition of the skin, hair and fingernails, and has also been implicated in the prevention of atherosclerosis and Alzheimer's disease [2–4,6–9]. The most important source of silicon for human is the diet (see Fig. 1).

2. The role of silicon in bone tissue

The role of silicon in the metabolism of bone tissue was first discovered by Carlisle in her studies on animals [10–13]. In young rodents, increased Si accumulation was found at sites of active mineralization of new tissue; the content of this element decreased with bone maturation. A relationship was also found between the content of silicon and calcium. Carlisle proved the significance of silicon to the process of skeletal development in a month-long experiment on chicks fed low- and high-silicon diets [11]. The animals fed diets supplemented with silicon (in the form of Na_2SiO_3) gained more weight and exhibited normal growth, while those deprived of a sufficient silicon intake revealed significant anomalies of skeletal development (lower bone mineralization and smaller size). Thus, silicon was shown to be an essential trace element indispensable for normal skeletal development, especially in the initial phase of bone formation. In addition, Schwarz reported the presence of a bound form of silicon in some mucopolysaccharides: hyaluronic acid, chondroitin 4-sulfate and heparan sulfate [14].

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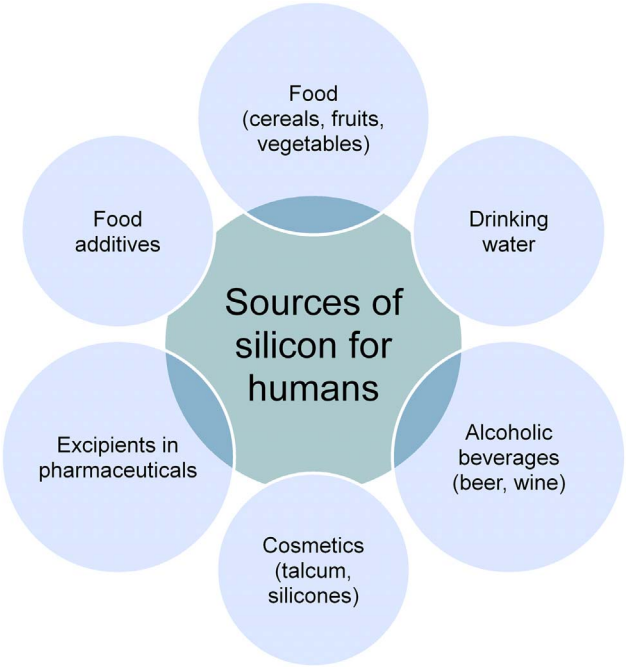

Fig. 1. Main sources of silicon for humans.

The publications cited above provided a starting point for wider-ranging research on the physiological functions of silicon in the development of bone tissue [15–24]. Further experiments on animals confirmed stimulating effects of silicon on bone formation. A study involving ovariectomized female rats (an animal model reflecting a loss of bone mass in postmenopausal women) showed that silicon supplementation reduces the degree of bone resorption, while increasing bone mineral density (BMD) [17]. In turn, a study examining female quarter horses fed zeolite A (a natural source of silicon) found a correlation between serum Si concentration and training distance to failure, indicating enhanced mechanical bone strength [18].

Extensive cohort studies have been carried out to establish the influence of silicon consumption by humans on BMD, which is responsible for the mechanical strength of bone tissue and is used as a diagnostic of osteoporosis. In the Framingham Offspring cohort consisting of 2847 individuals aged 30–87, a positive correlation was found between dietary silicon intake and BMD in males and premenopausal women. Differences between groups with the highest and lowest silicon intake (Si > 40 mg/day vs. < 14 mg/day, respectively) amounted to as much as 10%. However, such a correlation was absent in postmenopausal women, which suggests that the absorption and distribution of silicon may be affected by sex hormone levels [19].

The Aberdeen Prospective Osteoporosis Screening Study (APOSS) was conducted on perimenopausal and postmenopausal women aged 45–62 to elucidate the influence of dietary silicon intake on markers of bone metabolism. The study groups differed in terms of the use of hormone replacement therapy (HRT), whether currently or in the past. In contrast to the previous study, higher silicon intake was found to have a beneficial influence on BMD also in postmenopausal women, but only those treated with HRT, which shows a possible favorable interaction between silicon and estrogen (and especially estradiol) levels [20].

Supplementation with choline-stabilized orthosilicic acid (ch-OSA) in conjunction with calcium and vitamin D3 was evaluated in 136 osteopenic females (T-score < −1.5) by examining the effects of different doses of ch-OSA on markers of bone formation and BMD. The former included osteocalcin and procollagen type I *N*-terminal propeptide (PINP), while the resorption markers were deoxypyridinoline and collagen type I *C*-terminal telopeptide. At 12 months, the study found an increase in the bone formation markers, and in particular PINP, which is consistent with the literature data concerning the mechanism of action of Si [21].

Also experiments on tissue and cell cultures support a bone formation role for silicon. Reffitt et al. [22], who conducted extensive research on collagen synthesis, studied *in vitro* the relationship between orthosilicic acid concentration in the substrate and collagen type I synthesis by several cell lines (human osteosarcoma cell line MG-63, primary osteoblast-like cells derived from human bone marrow stromal cells and an immortalized osteoblast precursor cell line). The other measured parameters included collagen synthesis by fibroblasts, proline hydroxylase activity, alkaline phosphatase activity and osteocalcin production (reflecting osteoblast differentiation). Silicon was added to the medium in the amount of 10, 20, or 50 μM. The effect of silicon on proline hydroxylase was also investigated in the presence of its inhibitor. Collagen synthesis increased in all cell lines, with the optimal silicon content being 20 μM. In turn, alkaline phosphatase activity and osteocalcin synthesis were significantly higher at a silicon concentration of 10 μM, which indicates increased osteoblast differentiation; at the other studied concentrations the results were less favorable. A stimulating effect of silicon on collagen synthesis was not found in the presence of proline hydroxylase inhibitors, which suggests a mechanism of action involving proline hydroxylase activity regulation [22].

Another study, involving co-cultures of human dermal fibroblasts (HDF) and human umbilical vein endothelial cells (HUVEC), reported a stimulating effect of silicate ions on angiogenesis [23]. It should be noted here that adequate implant vascularization is prerequisite for the normal functioning and development of new tissue. The application of calcium silicate based material led to increased expression of vascular endothelial growth factor (VEGF) as well as VEGFR 2 receptor, which enhanced angiogenesis. Furthermore, it should be noted that VEGF exerts a beneficial effect on the level of bone morphogenetic protein, which regulates osteoblast growth and differentiation.

Mladenović et al. [24] examined the influence of silicon on the activity of osteoclasts, which are responsible for bone tissue resorption. Experiments on murine bone marrow showed inhibited osteoclast synthesis.

3. Silicon-substituted apatites as bone replacement materials

In clinical practice, silicon has been incorporated in a variety of biomaterials, mostly in the form of bioglasses and porous silica. These materials typically exhibit very good osseointegration capacity and rapid bioapatite generation on their external surfaces. The external regions of the biomaterial become hydrated, releasing silicate; this leads to high osteoblast activity and differentiation, as well as accelerated synthesis of collagen type I [16,25,26]. The possibility of incorporating silicate ions into the hydroxyapatite structure was extensively explored, amongst others, by Gibson et al. [27].

For many years now, HA has been used in reconstructive surgery due to its considerable similarity to the inorganic fraction of bone tissue, enamel, dentin and cementum, making it a biocompatible and non-toxic material. The crystallographic structure of HA enables partial substitution of calcium, orthophosphate and hydroxyl ions. Also biological apatite exhibits different patterns of substitution, due to which its actual composition is variable. In general, bioapatite is a calcium- and hydroxyl-deficient carbonate hydroxyapatite containing a range of ionic impurities, such as Na^+, K^+, Mg^{2+}, Zn^{2+}, HPO_4^{2-}, SiO_4^{4-}, Cl^- and F^- [25,26,28–31].

Since the 1990s, ion substitution in hydroxyapatite, and especially partial substitution of PO_4^{3-} with SiO_4^{4-}, has been widely applied in biomaterial engineering, largely due to the ease of this process [25,26].

According to the mechanism proposed by Gibson [27], when orthosilicate ions (SiO_4^{4-}) substitute phosphate ions (PO_4^{3-}), hydroxyl