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A REVIEW OF THE EFFECTS OF DIETARY SILICON INTAKE ON BONE HOMEOSTASIS AND REGENERATION.

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Abstract: *Objective:* Increasing evidences suggest that dietary Silicon (Si) intake, is positively correlated with bone homeostasis and regeneration, representing a potential and valid support for the prevention and improvement of bone diseases, like osteoporosis. This review, aims to provide the state of art of the studies performed until today, in order to investigate and clarify the beneficial properties and effects of silicates, on bone metabolism. *Methods:* We conducted a systematic literature search up to March 2013, using two medical databases (Pubmed and the Cochrane Library), to review the studies about Si consumption and bone metabolism. *Results:* We found 45 articles, but 38 were specifically focused on Si studies. Conclusion: Results showed a positive relationship between dietary Si intake and bone regeneration.

Key words: Dietary Silicon intake, Ortho-Silicic Acid, Bone regeneration, Osteoporosis, Silica scaffolds.

Introduction

Silicon (Si) is the second most common element in Earth's crust (28.9%), after Oxygen (45.5%). It represents the major trace element in the human body. In particular, highest Si concentrations are found in fast-growing cells such as hair, nails, bone and skin cells.

The major and most important source of Si, is the diet. Si daily intakes range from about 20mg/day to 50mg/day in Western countries. Higher intakes (104mg/day – 204mg/day), have been reported in China and India, where plant-based foods are the major components of the diet (1). About Si absorption, the main bio-available form, for human and animals, is the Ortho-Silicic Acid (OSA, SiOH4). It is well-known that Si in the form of OSA existing only in liquid, like mineral water and beer (2), but not in foods. Nevertheless, Si is hydrolized to OSA at the gastrointestinal level (3, 4). Among foods, highest Si levels are found in grains, especially oats, barley, white wheat flour and some rice fractions (5). Si is also present in the form of synthetic compounds or silicates, but they are rarely found in the diet.

As described in detail in the following paragraphs, several studies, performed both in vivo and in vitro, suggest that dietary consumption of Silicon is beneficial to bone health, playing an important role in bone homeostasis and regeneration and thus representing a potential trace element for the treatment and prevention of bone diseases, like osteoporosis (6-8). This pathology is considered a systemic heterogenic skeletal disease, which affects more than 200 million people in the world, characterized by an imbalance in bone turnover, leading to bone loss (osteopenia) and micro-architectural deterioration of bone tissue and increasing the risk of bone fractures. This disease typically occurs in postmenopausal or young women with estrogen deficiency (Type I) and in men and women older than 75 years (Type II). The etiology of osteoporosis is multi-factorial and involves genetic, hormonal, exercise related and nutritional factors, but also smoking, alcohol abuse and chronic intake of certain drugs, such as corticosteroids (9, 10).

However, the exact biological role(s) of Silicon in bone health is still not clear, although a number of possible mechanisms have been suggested, including the synthesis of collagen and/or its stabilization, and matrix mineralization. This review aims to provide an overview of this naturally occurring dietary element and the evidences of its potential role in bone health.

Materials and Methods

Two medical databases (Pubmed and the Cochrane Library), were used to analyze the literature. To facilitate the data collection and analysis, the articles were divided into three groups, as described below:

1) In vitro studies, on human and mouse cells;

2) In vivo studies, on osteoporotic patients and animal models;

3) In vivo and in vitro Silica based scaffolds studies;

For each categories, we evaluated the effects of Si supplementation on bone regeneration and homeostasis, considering the follow parameters:

- Number of animals/patients;
- Animals/patients health status;
- Amount of dietary Si intake;
- Bone mineral density and content;
- Bone volume, growth and length;
- Bone markers levels;
- Number and surface of osteoclasts and osteoblasts;
- Histological and/or molecular analysis

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Results and Discussion

From 1972 to 2013, thirty-eight articles about Si studies were found (Figure1a,b): eleven (29%) about Si studies on animal models, five (13%) about clinical studies on human, five (13%) concerned in vitro Si studies on cell cultures and seventeen (45%) regarded the development of Silica artificial scaffolds, both in vivo and in vitro. All these studies demonstrated the positive effect of dietary Si intake on bone health, suggesting the involvement of this important trace element in the early stages of bone formation. In fact, animal studies showed that supplementing with Silicon reduced the number of osteoclast (bone destroying) cells, partially preventing bone resorption and bone loss. Silicon compounds were also shown in vitro to stimulate the DNA synthesis in osteoblast (bone building) cells. Also human testing, in men and pre-menopausal women, demonstrated that dietary Si intake was positively associated with bone mineral density, reducing the risk of bone fractures.

In vivo Si studies

We divided in vivo Si studies into animal models and human studies, as described in detail in the following paragraphs.

Animal models

We found eleven articles about Si studies on animal models (Table 1): three (27%) performed on chickens (11-15), one (9%) on turkeys and seven (64%) on rats (Figure 1c). Chickens studies showed that Si deficiency resulted in bone defects, skulls abnormalities, reduction of the osteoblast number and of the bone matrix synthesis. Si effects were investigated both in normal and ovariectomized (OVX) rats. Normal rats studies, (17, 18), showed that the lack of Si in the diet caused a decrease in bone mineral content, supporting the importance of Si in bones mineral composition (especially femur and vertebra). About Si supplementation studies in OVX rats (16), the data reported showed that treatment with Silanol (a soluble organic Si) had beneficial effects on trabecular bone formation and volume, promoting osteoblast growth and enhancing bone matrix formation. Rico and collaborators (19) investigated the effects of dietary Si supplementation in OVX rats. The morphometric and densitometric analysis showed that Si inhibited the loss of bone mass in OVX rats, promoting the longitudinal growth of long bones, such as the femur. In a randomized controlled animal study on aged OVX rats, the Authors (20) showed that treatment with OSA, stabilized with Choline (ch-OSA), had a positive effect on bone turnover, reducing partial femoral bone loss. These data were similar to those obtained from Hott (16) and confirmed the important role played by Si, in bone mineralization. Other studies, have reinforced this hypothesis. One of these was performed in order to test the possible use of water-soluble Si, for the treatment of postmenopausal osteoporosis, using OVX rats as experimental model (7). Osteoporosis is characterized by a decrease in the rate of bone formation and an increase in bone resorption. In this study, the Authors reported an increase in bone formation and a decreased resorption, in Si treated animals, suggesting an augmentation in bone turnover. The positive relationship between Si supplementation and bone metabolism in OVX rats, was also reported by Kim and collegues (21), supporting the finding that Si is an essential trace element, useful in the prevention of osteoporosis and other bone diseases.

However, some negative Si effects were also reported (22), showing that treatment of rats and turkeys with very high Si doses, had deleterious effects in animals, causing a reduction in bone strength and elasticity.

Figure 1

(a) temporal distribution of Si studies between 1972 and 2013 (b) Percentage of Si studies between 1972 and 2013 (c) Si studies on animals (d) Si scaffolds experiments (e) In vitro Si scaffolds studies (f) In vivo Si scaffolds studies

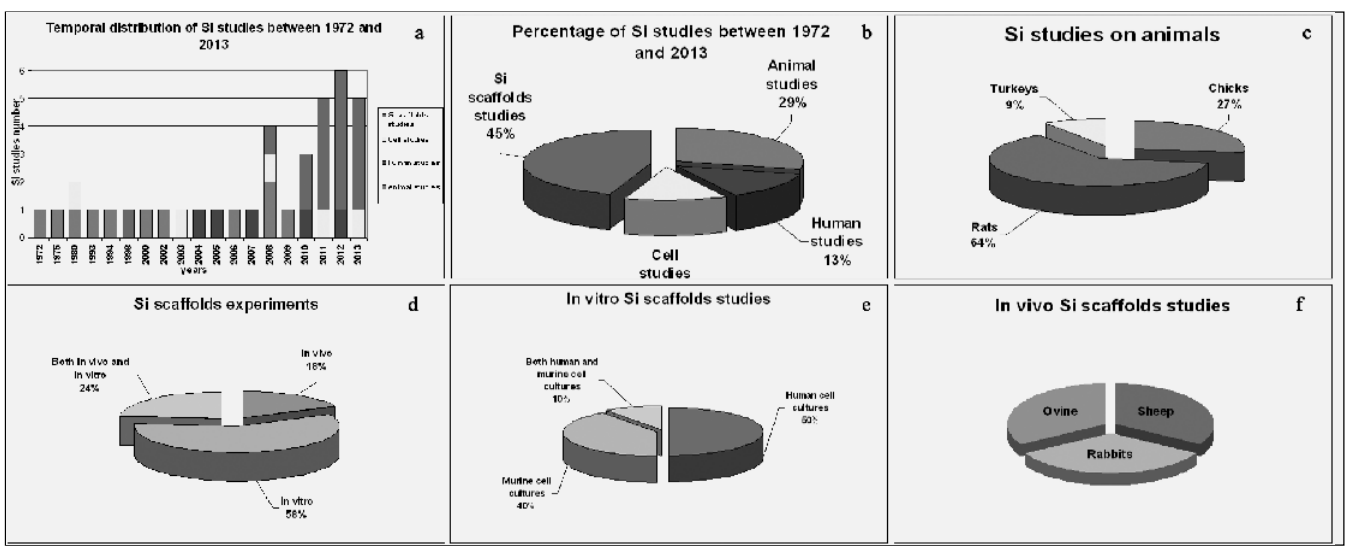

Table 1
Animal studies with Si dietary supplementation

AUTHORS	EXPERIMENTAL PROCEDURE	RESULTS
Carlisle 1972	Chicks fed with Si supplemented diet	↑ growth rate of chicks fed with diet supplemented with Si
Carlisle 1975	Chicks fed with a low Si diet	↓ amount of articular cartilage of tibia and femur bones
Carlisle 1980	Chicks fed with Si enriched diet	↑ normal skull formation
		↑ collagen levels
		↓ skeletal development
Hott et al. 1993	OVX rats fed with diet supplemented with	↑ osteoblast surface
	Silanol 0.1mg/kg day and 1mg/kg/day	↑ bone volume
		↓ osteoclast surface and number
		↓ bone loss
Seaborn et al., 1994	Effects of Si dietary supplementation on Rats	↑ BMD and bone mineral content
Rico et al.2000	OVX rats fed with diet supplemented with	↓ bone loss
	500 mg of Si	↑ longitudinal growth of long bones (femur)
Bae et al. 2008	OVX rats fed with diet supplemented with 20mg/kg/day of Si	↑ bone mineral density (BMD) of femur and tibia
		↑ bone markers formation (ALP, Osteocalcin)
		↓ osteoclast surface
Calomme et al. 2006	OVX rats fed with diet enriched with ch-OSA	↑ BMD and bone mineral content (BMC)
		↓ bone loss
Seaborn et al. 2002	Rats fed with diet supplemented with 35μg/g of Si	↑ skeletal growth
femur		↑ Ca+, K+ and Na+ concentration in the and tibia
		↑ bone mineralization
Kim et al. 2009	OVX Ca-deficient rats fed with diet	↑ BMD of femur and tibia
	supplemented with Si	↓ bone resorption biomarker CTx
Kayongo et al., 2008	Treatment of rats and turkeys with high Si doses	↓ in bone strength and elasticity.

Human studies

We found five clinical Si studies on human, especially on pre and post-menopausal women (Table 2). First population-based study on osteoporotic subjects (6), showed that 40 mg of daily intake of Silicon was associated with greater bone mineral density, reducing the risk of bone fractures. Similar observations were found in a subsequent study on post-menopausal women (23). The Authors analyzed the amount of Si adsorbed from foods and its influence on bone density, confirming the relationship between Si consumption and bone health and providing some insights into optimal Si intakes. In the same year, a group of osteoporotic subjects were treated with ch-OSA (24), demonstrating an increase in bone formation markers, especially PINP (pro-collagen type I N-terminal pro-peptide), a marker of collagen type I synthesis. Moreover, the Authors reported a significant increment in femur bone density. These observations were in agreement with those obtained from Calomme (20), in OVX rats. A subsequent work (8), was carried out in post-menopausal women, with the aim to investigate the absorption of Si from artesian drinking water and its effects on bone health. This study demonstrated that bottled water was a source of easily absorbed dietary Si. No significant effects on bone turnover were observed because of the short-term Si supplementation. In 2012, Mcdonald and collaborators (25), analyzed the association between Si and bone health, in early post-menopausal women, trying to understand if oestrogen (specifically estradiol) could interact with Si and influence bone status. Results indicated an interaction between Si and oestrogen, suggesting that oestrogen status was important for Si metabolism in bone health. However further investigations are needed to corroborate these evidences.

In vitro Si studies

We found five articles about in vitro Si studies (Table 3): one about Si effects in chondrocytes and tybial epiphyses of chick embryos, showing that Si stimulated bone matrix synthesis (14), and two about Si studies on the human MG-63 osteosarcoma cell line. Among these, one work (4) evaluated the in vitro effects of OSA (0-50μM), using the human MG-63

Table 2
Human studies with Si dietary supplementation

AUTHORS	EXPERIMENTAL PROCEDURE	RESULTS
Macdonald et al., 2012	Osteoporosis screening study to analyze the association between Si and bone health, in early post-menopausal women.	Si intake is positively correlated with BMD at the spine and significantly at the femur. Interaction between Si and oestrogen
McNaughton et al., 2005	Dietary Si intake in post-menopausal women and effects on bone.	↑ BMD (Bone mineral density)
Jugdaohsingh et al., 2004	Based population study (2847 subjects: 1251 men and 1596 women)	↑ BMD in hip and femoral neck
Spector et al., 2008	Randomized, placebo-controlled trial in osteopenic	↑ bone formation markers (PINP)
	female with ch-OSA dietary supplementation	↑ femoral BMD
Li et al., 2010	Study on post-menopausal women, to investigate	↑ collagen type I levels
	Si absorption from artesian drinking water and its effects on bone	↑ HOBs metabolic activity and proliferation

Table 3
In vitro Silicon studies

AUTHORS	EXPERIMENTAL PROCEDURE	RESULTS
Refitt et al., 2003	MG-63 and HCC1 cell lines treated with OSA (0-50μM)	OSA 10-20 μM: ↑ collagen levels and OSA 50μM has not significant effect
Kim et al., 2013	MC3T3-E1 cells treated with	↑ osteoblastic mineralization activity
	Sodium Metasilicate (0-100 μM)	↑ bone formation marker ALP
Shie et al., 2011	MG-63 cells treated with Si (0-6 mM)	Si 2 and 4mM: ↑ osteoblast proliferation
		Si 6mM: too high and ↑ cell death
Carlisle et al., 1980	Chondrocytes treated with Si	↑ bone matrix synthesis
Zou et al., 2008	Human osteoblast-like cells (HOBs) treated with Si (0-30 μM)	↑ HOBs metabolic activity and

osteosarcoma cell line and an immortalized human early osteoblastic cell line (HCC1), as osteoblast model, showing that physiological concentrations (10-20 μM) of OSA, promoted collagen type I synthesis and stimulated osteoblastic differentiation, both in MG-63 and HCC1 cells. On the contrary, at the highest concentration (50 μM), OSA caused a smaller increase in collagen type I synthesis. Similar results were obtained from Shie and colleagues (26), after the treatment of MG-63 cells with Si 0-6 mM, showing that the highest Si concentration increased cell death. In the other article (27), the Authors analyzed the role of Si, in form of Sodium Metasilicate, on the MC3T3 murine cell line, showing an increase in bone formation and mineralization. An additional study (28) evaluated the effects of silicate ions treatment on human osteoblast cells (HOBs), showing an increase of cellular metabolic activity and proliferation.

In vivo and in vitro artificial Si scaffold studies

The advent of nanotechnology has enabled the development of artificial scaffolds, increasing interest among the scientific community, due to their potential applications in the biotechnology and nanomedicine fields.

Based on the evidences of Si beneficial properties on bone health, artificial Si scaffolds have been generated, especially during the last years.

We found seventeen papers about Silicon-based scaffolds studies (Table 4a,b,c): ten (58%) were in vitro experiments, three (18%) were in vivo experiments and four (24%) were both in vivo and in vitro studies (Figure 1d). In vitro Si studies, were classified on the basis of the type of cell culture used. Five articles were performed on human cell cultures (hMSCs, MG-63, HOBs and SaOS-2 human cell lines), four on mouse cell cultures (MC3T3-E1, rBMSCs, 7F2 murine cell lines) and one on both human and mouse cells (Figure 1e). In the paragraph below, we have described in detail, these studies and their results.

The first in vitro Si scaffold experiment, using human cells, were performed on HOBs (Human primary Osteoblasts), to investigate the Si effects on cell growth and activity (29). Human osteoblasts were seeded on a thin layer of Silica gel and

Table 4a
In vitro studies with artificial Si scaffolds

AUTHORS	EXPERIMENTAL PROCEDURE	RESULTS
Anderson et al., 1998	Primary human osteoblasts (HOBs) seeded on a thin layer of Silica gel.	↑ osteoblast mineralization
Wiens and Wang, 2010	Human osteoblasts (SaOS-2) cultivated on biosilica substrates.	↑ osteoblast mineralization due to Si up-regulation of BMP-2 protein (bone morphogenetic protein 2)
Mieszawska et al., 2010	Human mesenchymal stem cells (hMSCs) grown on osteoinductive silk-silica composite biomaterials.	↑ of hMSCs proliferation and differentiation into osteogenic precursors ↑ of some osteogenic markers, as the Bone Sialoprotein (BSP) and the Collagen type 1 (Col 1).
Ganesh et al., 2012	Human mesenchymal stem cells (hMSCs) grown on Si scaffolds	↑ of hMSCs proliferation and differentiation into osteogenic precursors
Pelaez-Vargas et al., 2011	In vitro analysis of osteoblast-like MG63 human cells seeded on Zirconia (ZrO_2) substrates, coated with micropatterned Silica.	↑ osteoblast adhesion, growth and proliferation
Huangh et al., 2008 Midha et al., 2013	MC3T3-E1 murine cells were seeded and grown on Si and SiO_2 nanofiber coated scaffolds.	significant increase in cell growth and proliferation
Duan et al., 2012	rBMSC murine cells were seeded and grown on Si scaffolds.	↑ in rBMSC cell adhesion, proliferation and osteogenic differentiation.
Lehmann et al., 2012	Si scaffolds analysis both on osteoblasts murine cells (mOBs)) and on human cells (peripheral blood monocytes)	significant increase in cell growth and proliferation
Toskas et al., 2013	Use of the Osteoblastic 7F2 murine cells to evaluate cellular compatibility and bioactivity of an hybrid Si scaffold to bone tissue engineering.	The biomaterial promoted cells attachment and proliferation,confirming its potential use in bone repair and regeneration.

Table 4b
In vivo studies with artificial Si scaffolds

AUTHORS	EXPERIMENTAL PROCEDURE	RESULTS
Chaudhari et al., 2011	Authors investigated the osteoinductivity of silicate-substituted calcium phosphate in six female sheep.	Silicate substitution had a significant effect on bone formation.
Coathup et al., 2011	Study performed on New Zealand white rabbits, using Silica-based bioactive glasses.	Silica-based bioactive glasses had a significant effect on bone formation.
Coathup et al., 2013	Authors evaluated the osteointegration of silicate-substituted calcium phosphate (SiCaP) bone substitute materials, in an ovine critical-sized femoral condyle defect model.	Significant increase in bone formation

Table 4c
Both in vivo and in vitro studies with artificial Si scaffolds

AUTHORS	EXPERIMENTAL PROCEDURE	RESULTS
Beck et al., 2012	Evaluation of Si nanoparticles effects both in vivo in female mice (C57BL6) and in vitro on MC3T3 murine cells	In vivo ↑ bone mineral density In vitro ↑ osteoblast activity ↓ osteoclast number
Lee et al., 2011	Analysis of the effects on bone of a bioactive material containing Si and other elements, both in vivo in OVX rats and in vitro on MC3T3 and NIH3T3 murine cells.	In vivo ↑ bone regeneration In vitro ↑ of cell proliferation and differentiation
El-Gendy et al., 2012	Osteogenic differentiation of human pulp stromal cells on Si bioactive scaffold, both in vivo and in vitro	In vivo ↑ of osteogenic gene markers In vitro ↑ of bone tissue formation
Jun et al., 2013	Use of a Silica gel as a coating material to incorporate bone morphogenic protein-2 (BMP-2)	In vivo ↑ new bone formation In vitro ↑ of osteoblastic cellular responses

subsequently, cell activity, number and differentiation were measured at different times. Results showed an increase in bone mineralization, underlined by the presence of nodules on the Silica surfaces. Similar effects were obtained in a subsequent work (30) which showed a stimulation of mineralizing activity in human osteoblasts (SaOS-2), cultivated on biosilica substrates. According to this study, the use of biosilica scaffolds caused an upregulation of BMP2 (bone morphogenetic protein 2) expression, which promoted osteogenity in vitro. In the same year, Mieszawska and collaborators (31), obtained osteoinductive and biodegradable composite biomaterials for bone regeneration, by combining silk fibroin (a biomaterial extracted from Bombyx mori silkworm cocoons, used for in vivo and in vitro tissue engineering applications) and Silica particles. This type of scaffolds were used as substrate for the growth of human mesenchymal stem cells (hMSCs), showing an increase in hMSCs proliferation and differentiation into osteogenic precursors, confirmed by the up-regulation of some osteogenic markers, as the Bone Sialoprotein (BSP) and the Collagen type I. Similar results were obtained in another study based on the use of hMSCs and Si scaffolds (32).

MG63 human cells, were used to analyze cell behavior, when seeded on Zirconia (ZrO2) substrates, coated with micropatterned Silica [33]. In vitro analysis, showed that the silica films on ZrO2 were able to induce osteoblastic cell adhesion, spreading and propagation.

As regards in vitro Si scaffolds studies on mouse cell cultures, two were performed on the mouse osteoblastic cell line (MC3T3-E1) (34, 35), one on the rat bone marrow-derived mesenchymal stem cells (rBMSCs) (36) and another on the mouse osteoblastic 7F2 cell line (37).

Seeding the MC3T3-E1 cells on Si and SiO2 nanofiber coated scaffolds, the Authors showed a significant increase in cell growth and proliferation (34, 35). The study on rBMSC cells and Si scaffolds (36), showed an increase in cell attachment, proliferation and differentiation, suggesting that Si might be a promising material for bone regeneration. The mouse osteoblastic 7F2 cell line was used to evaluate the cellular compatibility and bioactivity of an hybrid Si scaffold (produced using Tetraethoxysilane as Si precursor) to bone tissue engineering (37). This biomaterial was proved cytocompatible when seeded with 7F2-cells, promoting attachment and proliferation and confirming its potential use as active biomaterials in bone repair and regeneration. We identify also one article (38) in which Si scaffolds were analyzed both on murine cells (mOB, murine neonatal bone-derived pre-osteoblasts) and on human cells (peripheral blood monocytes as osteoclast progenitors).

As concern in vivo Si scaffolds studies (Figure 1f), two articles were published in 2011 (39, 40) and one in 2013 (41). The first work [39], investigated the osteoinductivity of silicate-substituted calcium phosphate in six female sheep, showing a significant effect on bone formation. Similar findings were reported in a subsequent Si scaffold study (40), on rabbits. Two years later, Coathup and collaborators (41), evaluated the osteointegration of silicate-substituted calcium phosphate (SiCaP) bone substitute materials, in an ovine critical-sized femoral condyle defect model, showing a significant increase in bone formation. Four articles (42-45) were about both in vitro (on MC3T3-E1 and NIH3T3 murine cells) and in vivo (in mice and rabbits) Si scaffolds studies.

Conclusion

Based on these studies and their results, we can conclude that Si represents an essential trace element for bone health and homeostasis, leading to anti-aging, regenerating and reinforcing effects, useful in the prevention of bone diseases and in other biomedical applications, as tissue engineering and dentistry. The numerous Si studies performed until today, have contributed to define Si properties and to develop bioactive Silica-based materials, which represent successful solutions to different bone defects and diseases, due to their osteoconductive, osteoproductive and osteoinductive properties. Other advantages of Si scaffolds are the capacity to bond and integrate with living bone, without promoting toxicity or inflammation, the high reactivity and porosity. For these reasons, Si is increasingly considered as an ideal material for grafting, scaffolding, tissue repairing and regeneration.

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