Review Article

# Choline-Stabilized Orthosilicic Acid and Bone Health

**Ram Prabhoo**
Department of Orthopaedics, Mukund Hospital, Mumbai, Maharashtra, India

## Abstract

Certain trace elements play a very important role in bone health. Silicon is one such essential trace element required for bone regeneration, bone mineral density, and overall bone biology. Deficiency of silicon is associated with bone resorption rate, decreased osteoblastogenesis, increased osteoclastogenesis, reduced collagen, and glycosaminoglycan formation, suggesting a definite role of silicon in osteoporosis. Choline-stabilized orthosilicic acid (ch-OSA®) is a stable and bioavailable form of silicon. Due to its stable nature, it cannot be converted into nonabsorbable silica (polymerized) gel form. ch-OSA® is known to stimulate the enzymatic pathway of endogenous collagen synthesis. Silicon supplementation stimulates osteoblasts, osteoblastic differentiation, osteopontin, osteocalcin, alkaline phosphatase, and bone matrix mineralization. It inhibits bone resorption by reducing the surface area of osteoclasts. ch-OSA® has shown synergistic effects with calcium and Vitamin D, indicating its potential role in the management of osteoporosis. The aim of this review is to outline the importance of ch-OSA® on bone health.

**Key words:** Calcium, choline-stabilized orthosilicic acid, osteoporosis, silicon

**Address for correspondence:** Dr. Ram Prabhoo, Mukund Nagar Co Operative Housing Society, J B Nagar, Andheri Kurla Road, Andheri East, Landmark, Near Marol Pipe Line, Mumbai - 400 059, Maharashtra, India.
E-Mail: aprabhoo11@gmail.com

## Introduction

Silicon has received low prominence as a trace element and considered an inert universal element in the past. Silicon is widely present throughout the body with a strong predilection for bone and connective tissues.[1] Silicon is the second most and third most abundant trace element on the earth and in human body, respectively.[2] Silicon plays an essential role in the growth, development, and regeneration of various connective tissues of bones, cartilage, skin, etc.[3] Silicon is required for prolyl hydroxylase activation to synthesize collagen type-I. Reduced activity of another collagen synthesizing enzyme ornithine aminotransferase is associated with silicon deficiency. Glycosaminoglycans cross-linking require silicon in connective tissues.[4]

Bone is a connective tissue made up of osteoblast, osteoclast, osteocytes, bone lining cells, and various minerals.[5,6] Complex and well-organized framework of bone matrix is responsible for the mechanical strength of the bone.[7] Extracellular matrix of the bone is primarily composed of collagen type-I, glycoproteins, proteoglycans, and growth factors.[8] Almost 95% of the total collagen present in the bone and 80% of total proteins present in the bone are represented by collagen Type-I. Hydroxyapatite crystals in the form of spindle or plate shape are present in collagen fibers to make the bone matrix calcified, unlike other connective tissues. These hydroxyapatite crystals have a propensity to organize in the direction like the collagen fibers. An amalgamation of hydroxyapatite crystals (mineral phase) with collagen fibrils makes the collagen fibrils more hardened in bone tissues. The precise alignment in the form of quarter-staggered end-overlap of collagen molecules makes holes within the fiber for calcium apatite crystals nucleation followed by their growth in corresponding to collagen fibrils. Control of orientation and size of crystals are

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regulated by the arrangement and structure of collagen fibrils. The tensile strength of fibrils is increased by about twofolds and Young's modulus by about tenfolds due to the presence of collagen organic phase. Besides the presence of collagen and minerals, the orientation of collagen fibers also plays an important role in defining mechanical properties of bone. The mechanical properties of bone alter with age due to changes in the content of minerals and collagen. Quality of bone is not only determined by its mineral content. Mineral provides stiffness, strength, and mechanical properties and acts as an ion reservoir. Organic component predominantly made up of type-1 collagen provides elasticity, toughness, flexibility, and mechanical properties to the bones.[9] Osteopenia and osteoporosis are associated with weak bones and increased susceptibility to fractures due to microarchitectural deterioration of bone tissue and low bone mass.[10]

## Markers of Bone Turnover[11]

Bone undergoes continuous remodeling process throughout life that involves bone resorption for approximately 10 days followed formation for approximately 3 months in a sequential manner. The biomolecules released into the circulation during this process are called as bone turnover markers. Bone turnover markers are classified as:

1. Bone formation biomarkers
2. Bone resorption biomarkers.

### Bone formation biomarkers

These are produced by active osteoblasts during different phases of the bone formation process. Most commonly known bone formation biomarkers are

- Procollagen type 1 propeptides, for example, procollagen Type 1 N-terminal propeptide (PINP) and procollagen Type 1 C-terminal propeptide (P1CP)
- Osteoblast enzymes: Alkaline phosphatase (ALP)
- Matrix proteins: Osteocalcin (OC).

### Bone resorption biomarkers

These are synthesized by active osteoclasts during bone resorption phase at the time of the bone resorption process. They are classified as

- Collagen degradation products: Carboxy-terminal collagen crosslinks-1 (CTX-1), CTX-matrix metalloproteinases (CTX-MMP), amino-terminal collagen crosslink-1 (NTX-1), hydroxyproline, pyridinium crosslinks (PYD), deoxypyridinoline (DPD), etc
- Non collagenous proteins: bone sialoprotein
- Osteoclastic enzymes: Tartrate-resistant acid phosphatase, cathepsin-K
- Osteocyte activity markers: Receptor activator of nuclear factor kappa-B ligand, osteoprotegerin, Dickkopf-related protein-1, and sclerostin.

### Silicon and bone health

Bone formation and maintenance requires silicon.[12] Silicon has a direct effect on the synthesis of bone matrix and facilitates bone calcification and mineralization.[13] An increase in bone mineral density (BMD) and bone strength is related to increased consumption of bioavailable silicon.[12] Silicon intake also improves cortical bone health.[12]

### Silicon and collagen synthesis

Silicon positively influences endogenous collagen synthesis by stimulating activities of certain enzymes involved in the process of collagen synthesis. Collagen type-I synthesis is a series of closely harmonized physiological process. Adequate silicon concentration is required for the activation of prolyl hydroxylase that catalyzes the proline residues of collagen chains which is a critical step in collagen type-I synthesis and its secretion into the extracellular space.[3,14] Prolyl hydroxylase enzyme gets activated by silicon in osteoblast cytoplasmic granular endoplasmic reticulum followed by bone formation and mineralization.[15]

## Consequence of Silicon Deficiency on Bone Health [Figure 1] [16,17]

### Conventional silicon and poor bioavailability

Silicon is present in various forms in nature. Silicon presents in the form of orthosilicic acid (OSA) in water and beverages, in the form of unhydrolyzed polymeric (nonabsorbable) silica in plants, and in the form of silicates in soils or as a food additive. OSA has an uptake of greater than 50% of the consumed dose in humans suggesting its high bioavailable nature. However, due to unstable nature, OSA gets polymerized excessively at higher concentrations, making it poorly bioavailable. To overcome the challenges related to stability and bioavailability, efforts are made to develop OSA as a stable and bioavailable form at high concentrations.[3,4,13,18]

### Introduction to choline-stabilized orthosilicic acid

Choline-stabilized orthosilicic acid (ch-OSA®) has a unique ability of influencing collagen synthesizing enzymes to generate endogenous collagen production in the body.[3] It is also a stable and bioavailable form of OSA with proven clinical benefits on bones and joints.[19,20]

### Choline-stabilized orthosilicic acid stabilization technology

OSA is a soluble and absorbable form of silicon, but it must be stabilized to prevent its polymerization into polysilicic

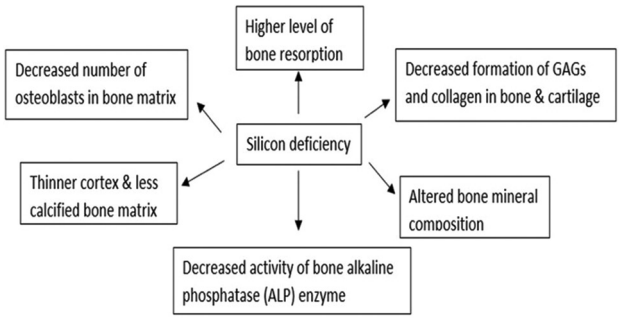


**Figure 1:** Impact of silicon deficiency on bone health.[17,18]

acids and eventually into silica gel, resulting in a decreased silicon bioavailability. OSA stabilization technology is the most advanced technology involving the use of choline as an ideal stabilizer to make OSA as a most bioavailable form of silicon. Choline chloride forms hydrogen bonds with OSA to form a stable, soluble, and most bioavailable form of silicon by preventing extensive polymerization and aggregation of silicon particles.[20] Apart from its role as OSA stabilizer, choline plays many important roles in various physiological processes of the body which includes phospholipids precursor, cellular signaling, lipid metabolism, and inhibition of homocysteine-mediated collagen destruction.[2]

## Mechanism of action of Choline-Stabilized Orthosilicic Acid (Silicon) [Figure 2] [13,16,17]

### Role of choline-stabilized orthosilicic acid in collagen synthesis [Figure 3][3]

#### *Absorption and bioavailability of choline-stabilized orthosilicic acid*

An ingested form of silicon and degree of formation of soluble and absorbable form of silicon in the gastrointestinal (GI) tract are the determinants of silicon absorption. OSA can easily permeate across the mucus layer due to its very weak or no interaction with the mucus layer owing to its uncharged nature. Its major uptake by energy-independent paracellular pathway or small pore transcellular pathway occurs at the proximal small intestine facilitated by leading to its rapid absorption profile. Polymeric or colloidal species of silica cannot be easily broken down in the GI tract leading to its nonsignificant absorption profile.[1]

#### *Excretion of choline-stabilized orthosilicic acid*

Absorbed form of silicon is excreted mainly by the kidney with rapid filtration with small tubular re-absorption.[21] Silicon in the form of neutral OSA rapidly disseminates into red blood corpuscles and other tissues.[1] Clinical study has shown that ch-OSA® has higher bioavailability with a significant increase in serum silicon concentration compared to other silicon-containing formulations.[22]

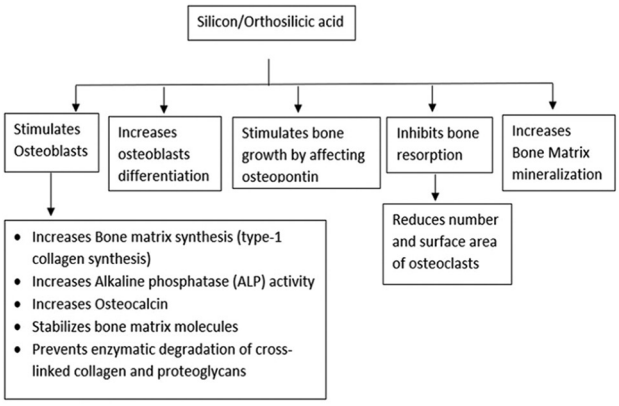


**Figure 2:** Mechanism of action of choline-stabilized orthosilicic acid in bone health.[13,17,18]

## Experimental Studies of Choline-Stabilized Orthosilicic Acid

Reffitt *et al*. 2003 had performed an *in vitro* study to evaluate the ability of OSA in stimulating the synthesis of collagen type-1 using different cell cultures like Human osteosarcoma cell line (MG-63), primary osteoblast-like cells derived from bone marrow stromal cells, and immortalized clonal human bone marrow cell-like homogeneous charge compression ignition (HCCI). The study showed statistically significant ($P < 0.05$) increase in collagen type 1 synthesis with the treatment of ch-OSA® at different concentrations Si 10 µM, Si 20 µM, and Si 50 µM compared to control group on MG-63 cell lines, HCC1 cell line as well as primary osteoblast-like cells. Moreover, ch-OSA® treated group showed a statistically significant ($P < 0.05$) increase in ALP activity and OC synthesis on MG-63 cell lines.[13]

Another *in-vitro* study was conducted by Arumugum MQ *et al* 2004, to evaluate the effect of ch-OSA® on collagen type-1 gene expression on cultured human trabecular bone-derived osteoblasts cells human osteoblast cells (HOBs). The study showed a statistically significant ($P < 0.05$) relative increase in collagen type 1 mRNA expression level in human osteoblast cells (HOBs), indicating a positive effect of OSA on collagen type-1 synthesis.[23]

Calomme *et al*. 2006 had evaluated the efficacy of ch-OSA® on bone loss in aged ovariectomized (OVX) rats. The study

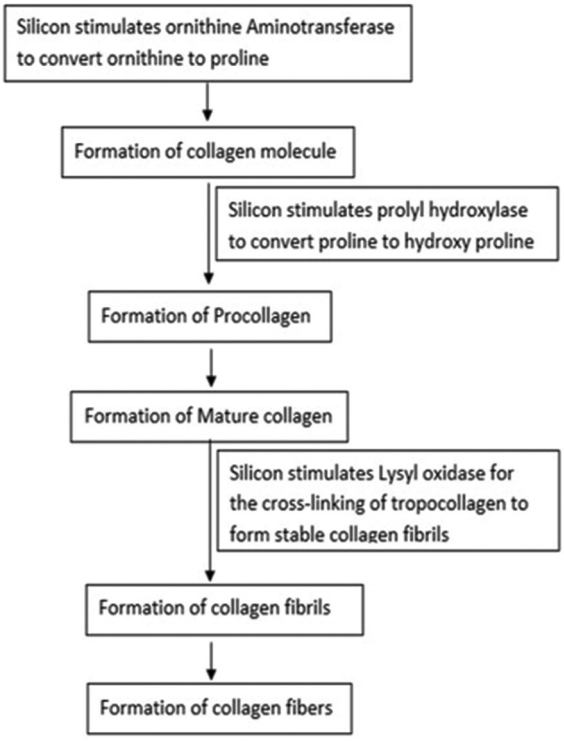


**Figure 3:** Stimulation of collagen synthesis pathway by choline-stabilized orthosilicic acid.[3]

consisted of SHAM control (no estrogen deficiency), OVX "0" control (estrogen deficiency) and OVX "1" (estrogen deficiency and treated with ch-OSA® at the dose of 1 mg Si/Kg body weight for 30 weeks of duration. Treatment with ch-OSA® showed a significant increase in BMD at midshaft and distal metaphysis region compared to other groups, suggesting an important role of ch-OSA® in bone metabolism and bone health.[16]

Kim *et al*. 2017 had evaluated the effect of OSAOSA in the expression of collagen type-1, Wnt-3α, and β-catenin protein. Wnt-3α and β-catenin protein was increased in OSA group and type I collagen expression was increased 2.5-fold in the OSA group.[24]

Chi *et al*. 2019 had reported the ability of OSA to promote osteoblast differentiation and mineralization using two representative murine preosteoblast cell lines (C2C12 and MC3T3-E1). OSA concentration above 10 μM and up to 20 μM had increased ALP activity and expression of the autophagy-related factors sequestosome-1/p62. This study has reported autophagy as a novel mechanism of OSA in promoting differentiation and mineralization of osteoblastic cells.[25]

Zhou *et al*. 2019 had described the potential of OSA to promote osteogenesis by activating PI3K-Akt-mTOR pathway using osteoblast-like cell lines such as MG-63 and U2-OS. They had also increased other osteogenic markers like type I collagen, alkaline phosphatase, OC, and P1NP, suggesting its potential role in the osteogenesis process.[26]

## Clinical Studies of Choline-Stabilized Orthosilicic Acid/Silicon

Spector *et al*. 2008 had conducted a double-blind, placebo-controlled study to evaluate the effect of ch-OSA® on the markers of bone formation and BMD in 184 women with a mean age 60.7 ± 10.4 years for 1 year of duration. This clinical study consists of four Groups (1) 3 mg Si as ch-OSA®/d and 1000 mg calcium + Vitamin D3 800 IU/d; (2) 6 mg Si as ch-OSA®/d and 1000 mg calcium + Vitamin D3 800 IU/d; (3) 12 mg Si as ch-OSA®/d and 1000 mg calcium + Vitamin D3 800 IU (Vitamin D3)/d; and (4) 1000 mg calcium + Vitamin D3 800 IU (Vitamin D3)/d. Treatment with ch-OSA® resulted in a significant increase in the synthesis of collagen type-1 biomarker, i.e., PINP level as well as increase in femur BMD ($P < 0.05$) compared to the group received only calcium and Vitamin D3 indicates potential beneficial effect in osteoporosis management. No significant changes in the biochemical serum and urine parameters were observed in ch-OSA® treated group. This suggests the supplementation of ch-OSA® for 1 year found to be safe and well tolerated.[19]

Jugdaohsingh *et al*. 2004 conducted a cross-sectional, population-based study to evaluate the effect of dietary silicon on BMD in men and premenopausal women and found the positive effect of silicon intake on cortical bone BMD.[27]

Macdonald *et al*. 2012 had reported the ability of silicon to increase bone formation biomarker P1NP level and to reduce the level of bone resorption biomarkers free pyridinoline and deoxypyridinoline cross-links relative to creatinine (fPYD/Cr and fDPD/Cr) to improve the bone health.[28]

Macdonald *et al*. (2005) showed that silicon intake was associated with a significant increase in BMD at the hip and lumbar spine in premenopausal and postmenopausal women.[29]

Vigna *et al*. (2019) reported the beneficial effect of silicon supplementation in the prevention of osteoporosis in postmenopausal women due to its antioxidant property. They had reported a significant reduction in bone resorption biomarker DPD and improved oxidative status which can be a complementary treatment for an early phase of BMD reduction.[30]

Calomme *et al*. (2000) conducted a double-blind clinical study in 14 healthy subjects aged 22–34 years to evaluate the absorption and urinary excretion profile of silicon from ch-OSA® in comparison with other herbal silica and colloidal silicic acid. The study consisted of four groups: Group-1 received 20 mg Si per oral in the form of ch-OSA®, Group-2 received 533 mg of dry Equisetum arvense extract, Group-3 received colloidal silicic acid 2 ml of H2Sio3/ l, and Group-4 was a placebo group. The study showed a significant increase in serum Si concentration (54 μg/ml; $P < 0.005$) from baseline value after 1 h after ch-OSA® supplementation. Moreover, ch-OSA® supplemented group showed higher mean AUC ($P < 0.002$) compared to other sources of silicon, indicating higher bioavailability of Si from ch-OSA® source.[22] Renal clearance is a measured route of silicon excretion. The bioavailability of silicon is largely dependent on its chemical form.[23]

Choi *et al*. (2016) had shown a positive correlation between dietary silicon intake and increase in activity of bone formation biomarker serum total ALP.[31]

### Safety of choline-stabilized orthosilicic acid

Ch-OSA® has safety approval from the European Food Safety Authority.[32] A randomized double-blind placebo control trial of ch-OSA® conducted for 1 year has shown the safety of ch-OSA® on various parameters such as glucose, urea, creatinine, uric acid, ferritin, total proteins, cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total bilirubin, Serum Glutamic-Oxaloacetic Transaminase (SGOT) (aspartate aminotransferase), Serum Glutamic Pyruvic Transaminase (SGPT) (alanine aminotransferase), SGOT/SGPT, Gamma-Glutamyl Transpeptidase (GGT), cholinesterase, amylase, lipase, trypsin, sodium, potassium, calcium, phosphorus, copper, magnesium, zinc, Vitamin D3, ketones, urobilinogen, nitrite, leukocyte esterase, pH, creatinine kinase, and total proteins.[20] ch-OSA® has been approved for human consumption and is known to be nontoxic. Its lethal doses exceed 5000 mg/kg body weight in humans.[19]

## Summary

Ch-OSA® is a stable and bioavailable form of silicon with an ability to stimulate endogenous collagen production, stimulation of osteoblastogenesis and inhibition of osteoclastogenesis makes it a novel therapeutic option in addition to calcium and Vitamin D therapy in the management of osteoporosis.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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